Management of various Disorders of Sex Development (DSD)

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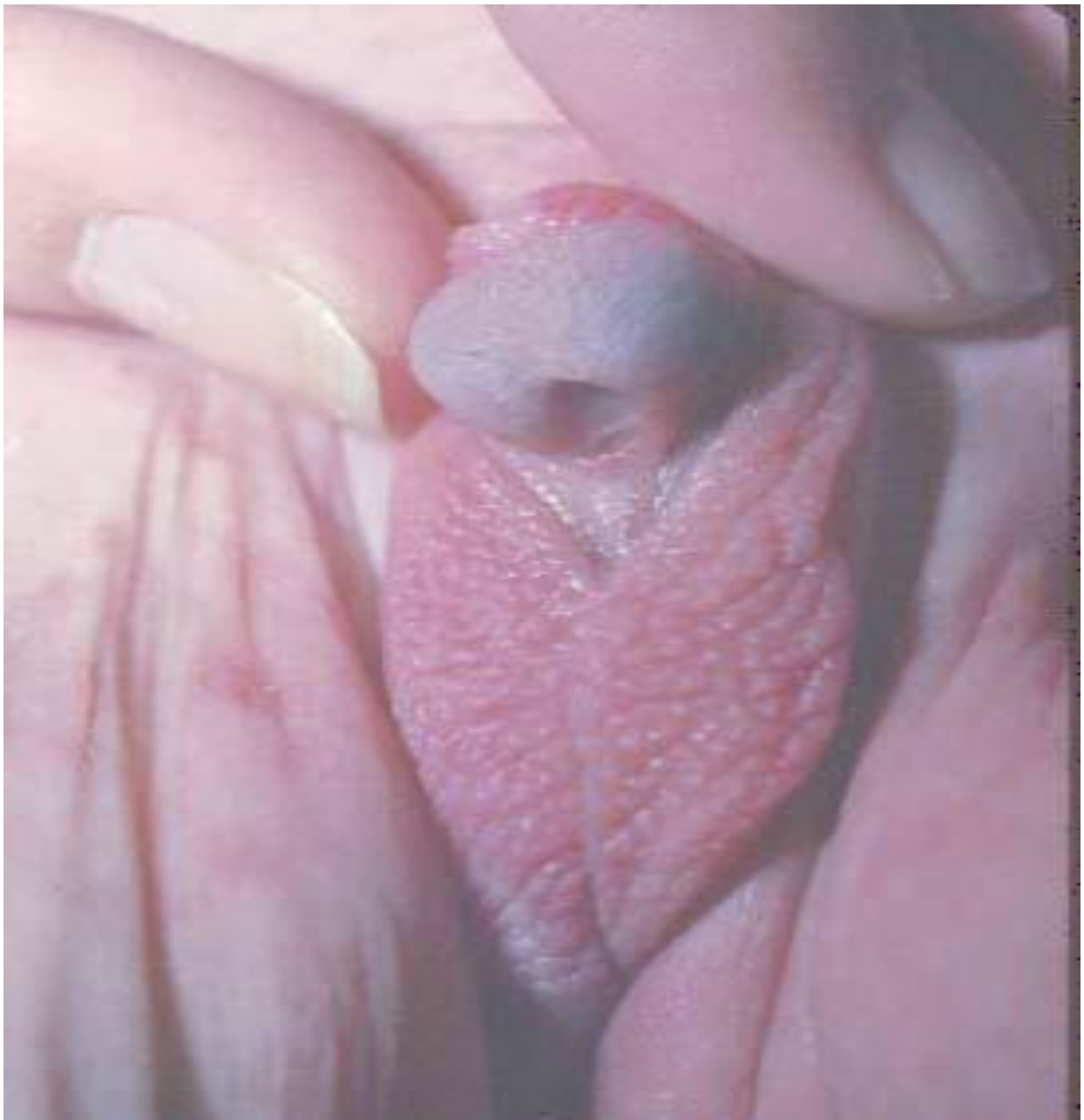
“ Is it a boy or a girl ?”

- The birth of an intersex infant is often viewed as a major crisis by parents & other family members

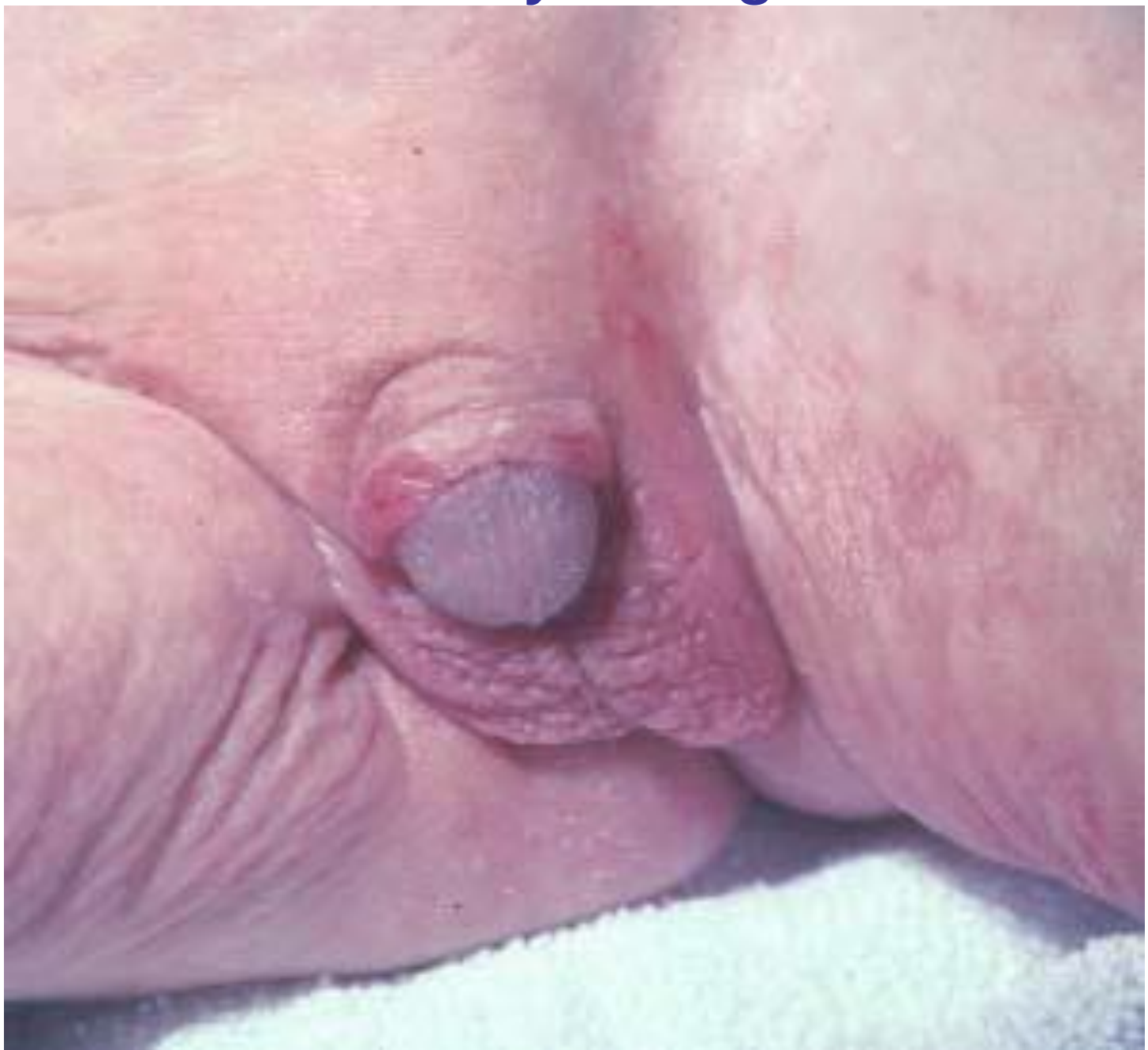
- Pediatric endocrinologists can offer valuable support by helping the parents to understand sex differentiation & medical / surgical options that are available for their child

- Specifically, should inform parents about:
  - long-term cosmetic & functional outcomes associated with genital reconstruction
  - the need for long-term sex hormone replacement
  - possibilities for reproduction

Is it a boy or a girl ?



Is it a boy or a girl ?



The multidisciplinary team management

Medical
Surgical
Psychological

Management of Congenital Adrenal Hyperplasia

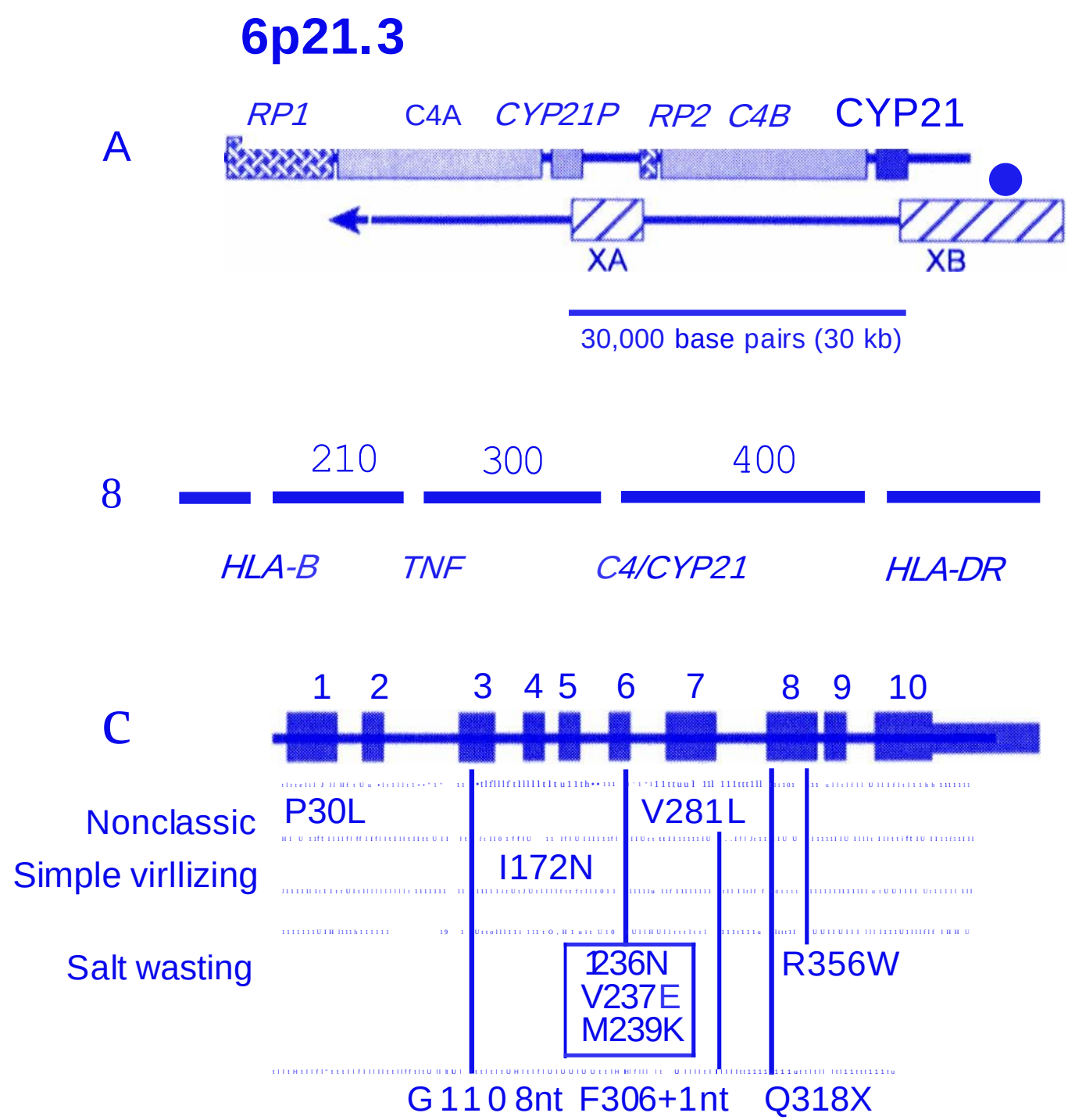
1. Classical form (presentation since birth)

2. Non – classical form (presentation in childhood / adolescence due to mild enzyme deficiency)

3. Severe classical form (with almost complete deficiency of enzymes “ Null mutation”)

Genetics of 21- Hydroxylase Deficiency (Example for CAH)

- The gene encoding 21 hydroxylase (microsomal cytochrome P450) is called CYP21
- Located on the short arm of chromosome 6
- So far, 50 mutations in the CYP21 have been identified
- In general, there is a good correlation of genotype to phenotype (I.e correlation of the disease severity and the type of mutation)

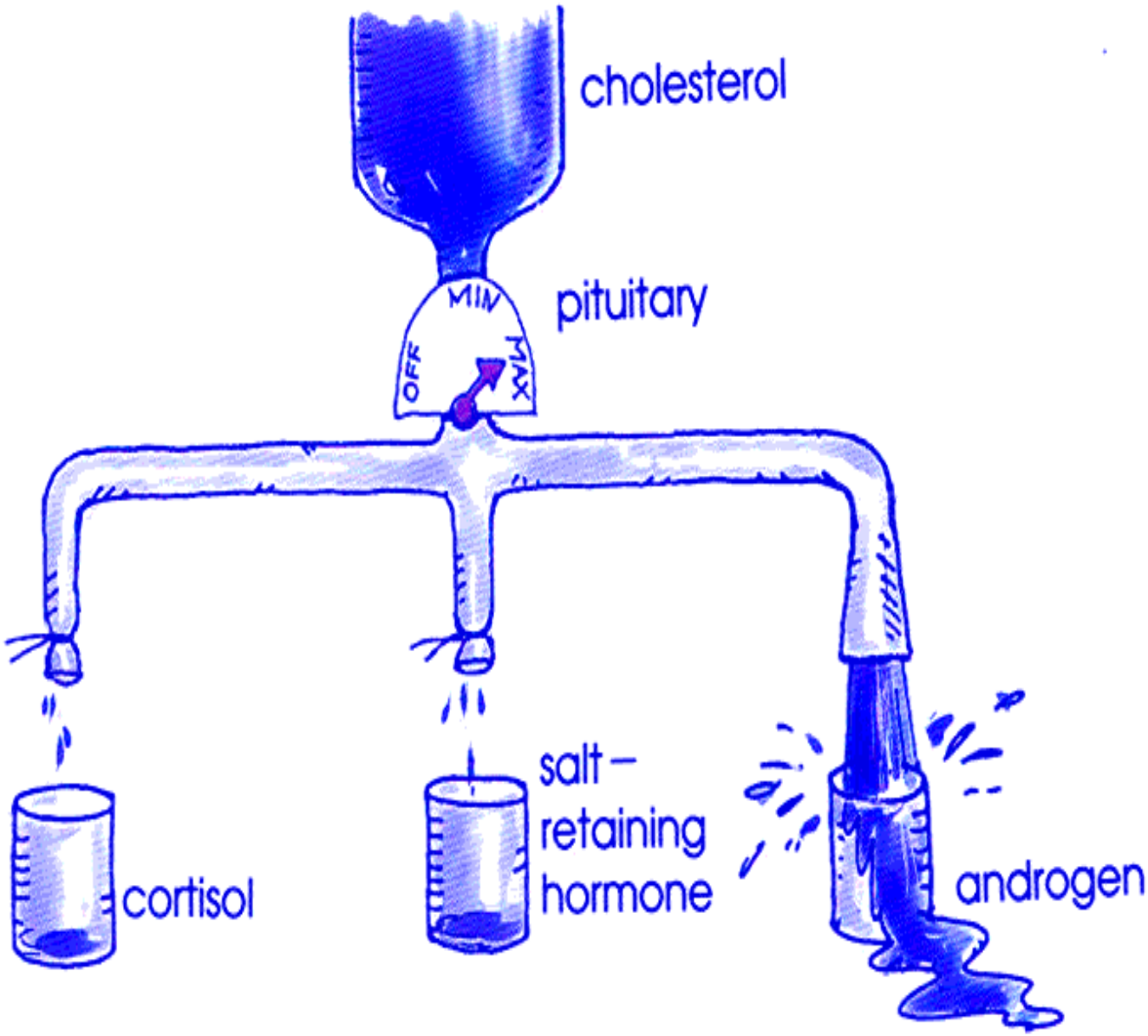

6p21.3
A
RP1
C4A
CYP21P
RP2
C4B
CYP21
XA
XB
30,000 base pairs (30 kb)
8
210
300
400
HLA-B
TNF
C4/CYP21
HLA-DR
C
1
2
3
4
5
6
7
8
9
10
Nonclassic
Simple virllizing
Salt wasting
P30L
I172N
V281L
I236N
V237E
M239K
R356W
G 1 1 0 8nt
F306+1nt
Q318X

Management of Congenital Adrenal Hyperplasia

Classical form (presentation since birth)

- Commonest enzyme deficiency is 21-hydroxylase
- Leads to the accumulation of:
  - 17- hydroxyprogesterone
  - Adrenal androgens (Androstendione, DHEA, DHEAS)
  - Decreased production of glucocorticoid ± mineralocorticoid (salt wasting type)
- In salt-wasting CAH, additional severe renal salt loss occurs as a consequence of aldosterone deficiency

Congenital Adrenal Hyperplasia



Overproduction of androgens causes:

- Virilization
- Advanced skeletal maturation & early epiphyseal fusion
- Accelerated growth in childhood with final short as adult

- Management consists of substitution of cortisol ± aldosterone **AND** reduction of excessive androgen production
- Management of children with CAH is challenge to the endocrinologist regard to growth outcome

Management

- Hydrocortisone 10-15 mg/m^2/day divided into 3 doses
- In infancy & early childhood, additional sodium replacement is required together with
- Fludrocortisone 0.05 - 0.2 mg / day (in salt – losing types)
- Monitoring of growth, signs of androgen excess, pubertal development & blood pressure

Glucocorticoid replacement

- In children, the preferred cortisol replacement is hydrocortisone in doses of 10 - 15 mg/m2/day in 3 divided doses (not 2 doses as short half life of hydrocortisone).
- These doses exceed physiological levels of cortisol secretion, which are 6–7 mg / m^2/day in children
- The supra-physiological doses given to children with CAH seem to be required to adequately suppress adrenal androgens & to minimize the possibility of developing adrenal insufficiency

- The short half-life of hydrocortisone minimizes growth suppression & other adverse side effects in comparison to longer acting, more potent steroids such as prednisone & dexamethasone
  - Challenge is !!
- There is only a narrow therapeutic window in the treatment of CAH with glucocorticoid

- Older adolescents & adults may be treated with modest doses of prednisone (5–7.5 mg daily in
  - 2 divided doses) or dexamethasone (0.25–0.5 mg given as 1-2 daily).

- In over treatment with steroids (Iatrogenic Cushing's syndrome)
  - Short stature
  - Truncal obesity
  - Osteoporosis
- Over treatment is a greater risk when potent longer acting glucocorticoid (e.g. prednisone, or dexamethasone when are used in childhood)
- Under treatment with steroids leads to:
  - Androgen excess with advancement of bone age, and reduced final height due to early epiphyseal closure

- Patients should be monitored carefully for signs of iatrogenic Cushing's syndrome such as:
  - Rapid weight gain
  - Short stature
  - Hypertension
  - Pigmented striae & osteopenia

- Treatment efficacy (suppression of adrenal hormones) is assessed by monitoring of:
  - ACTH (preferably at 0800 am" physiological peak"
  - 17-OHP
  - Androstenedione levels
  - Testosterone is useful parameter in females & prepubertal males

- Children should have annual bone age x-ray & careful monitoring of linear growth

- Despite careful monitoring & good patient compliance, most retrospective reviews indicate that final height averages 1–2 SDS below the population mean or the target height based on parental heights

- Hydrocortisone dose > 15 mg / m^2/ day is potentially detrimental to growth

Stress dosing

- Dose guidelines include tripling the maintenance dose of oral hydrocortisone (administered in three divided doses) in minor febrile illnesses.
- If a patient is unable to tolerate oral medication, intramuscular hydrocortisone may be given.
- For major surgery, administration of hydrocortisone (100 mg / m^2/ day) divided into 4 intravenous doses is warranted for at least 24 h peri & postoperatively before tapering over several days to a maintenance dose.

Prenatal treatment

- Only mothers at risk for 21-hydroxylase deficiency.
- Start treatment when pregnancy is confirmed.
- Not after 9 weeks of gestation.
- Dexamethasone 0.5mg TDS (not exceed 20 mcg/kg/d).

Stop treatment:

- Male sex.
- Unaffected female fetus (normal 17OHP & genotype).

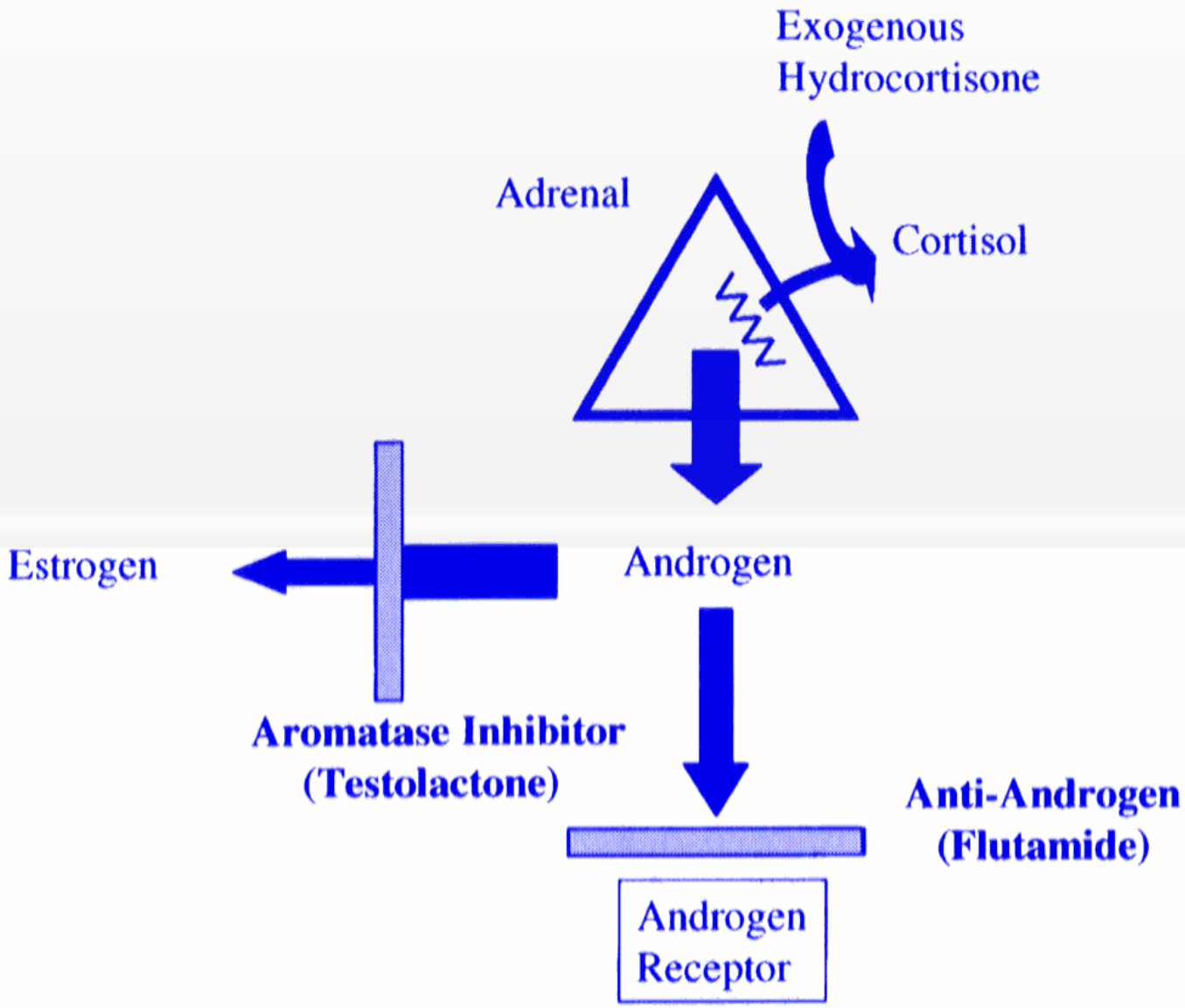
Management of Congenital Adrenal Hyperplasia

Severe classical form (with almost complete deficiency of enzymes “ Null mutation”)

Polypharmacy therapy approaches

- Instead of using high-dose hydrocortisone in order to suppress excessive androgens, to use lower doses of hydrocortisone together with anti-androgens & aromatase enzyme inhibitors

Poly Pharmacy Therapy



Anti -Androgens

Intra – Adrenal blockage of androgen production

- Ketoconazole
  - Blocks adrenal steroid production at several enzymatic steps
  - Considered to be " reversible medical adrenalectomy"

Peripheral blockage of androgen action

- Spirinolactone (aldactone)
- Cyproterone acetate (Androcur)®
- Finasteride : 5 α- reductase enzyme inhibitor
- Flutamide: Androgen receptor-blockers

Aromatase Enzyme (CYP19)

- Aromatase enzyme is the enzyme responsible for the last step of estrogen biosynthesis

- Aromatase enzyme converts
  - Androstedione to estrone
  - Testosterone to estradiol

- Converts testosterone into estradiol

Aromatase Inhibitors

- Testolactone (Teslac) is a competitive steroidal aromatase inhibitors
  - Dose 20 mg/kg/day initially then 40 mg/kg/day divided into 4 doses
  - Letrozole (Femara)® is a non-steroidal aromatase inhibitor (lowers estrogen production) used to treat breast cancer and in any disorders to reduce estrogen production in order to delay closure of the epiphysis.
- Anastrozole (Arimidex)®
  - 3rd. generation Aromatase inhibitor
  - more potent & specific inhibitors of aromatase enzyme

Bilateral Adrenalectomy

- Bilateral adrenalectomy has been proposed recently as surgical treatment option for severe classical form of congenital adrenal hyperplasia
- To date, few operations have been reported; all were done in difficult-to-control cases

Gene therapy

- Because 21-hydroxylase deficiency is an inherited metabolic defect, the question arises of the feasibility of gene therapy
- High level expression would need to be targeted to the adrenal cortex, where adequate levels of steroid precursors are available.
- As the most difficult therapeutic goal to achieve is adequate suppression of adrenal androgens, expression would need to be sufficiently high to permit nearly normal levels of cortisol biosynthesis under both normal and stress conditions, and such levels of expression would need to be maintained indefinitely to be cost effective in comparison with conventional treatment.
- These criteria seem unlikely to be met for the foreseeable future

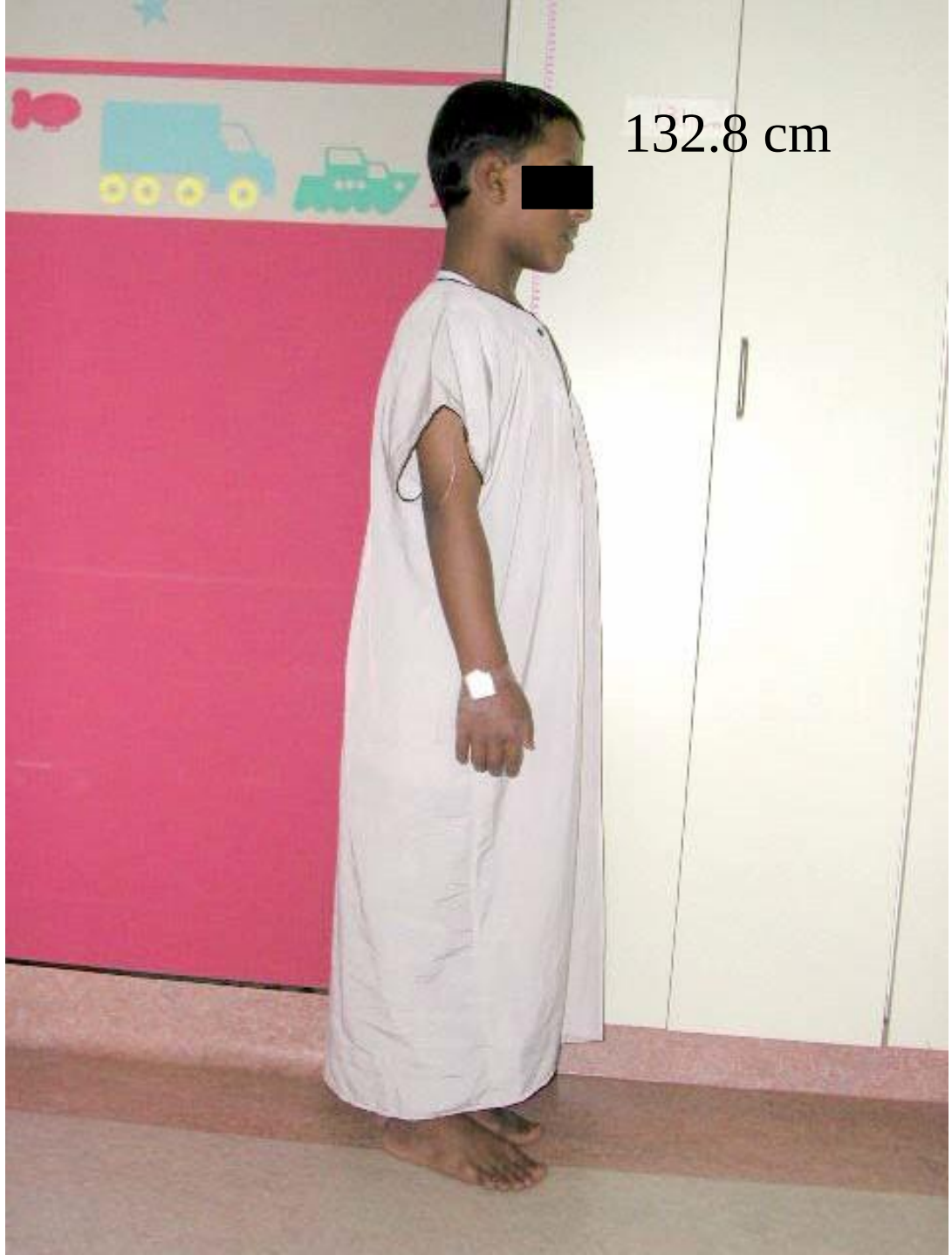
Management of Congenital Adrenal Hyperplasia

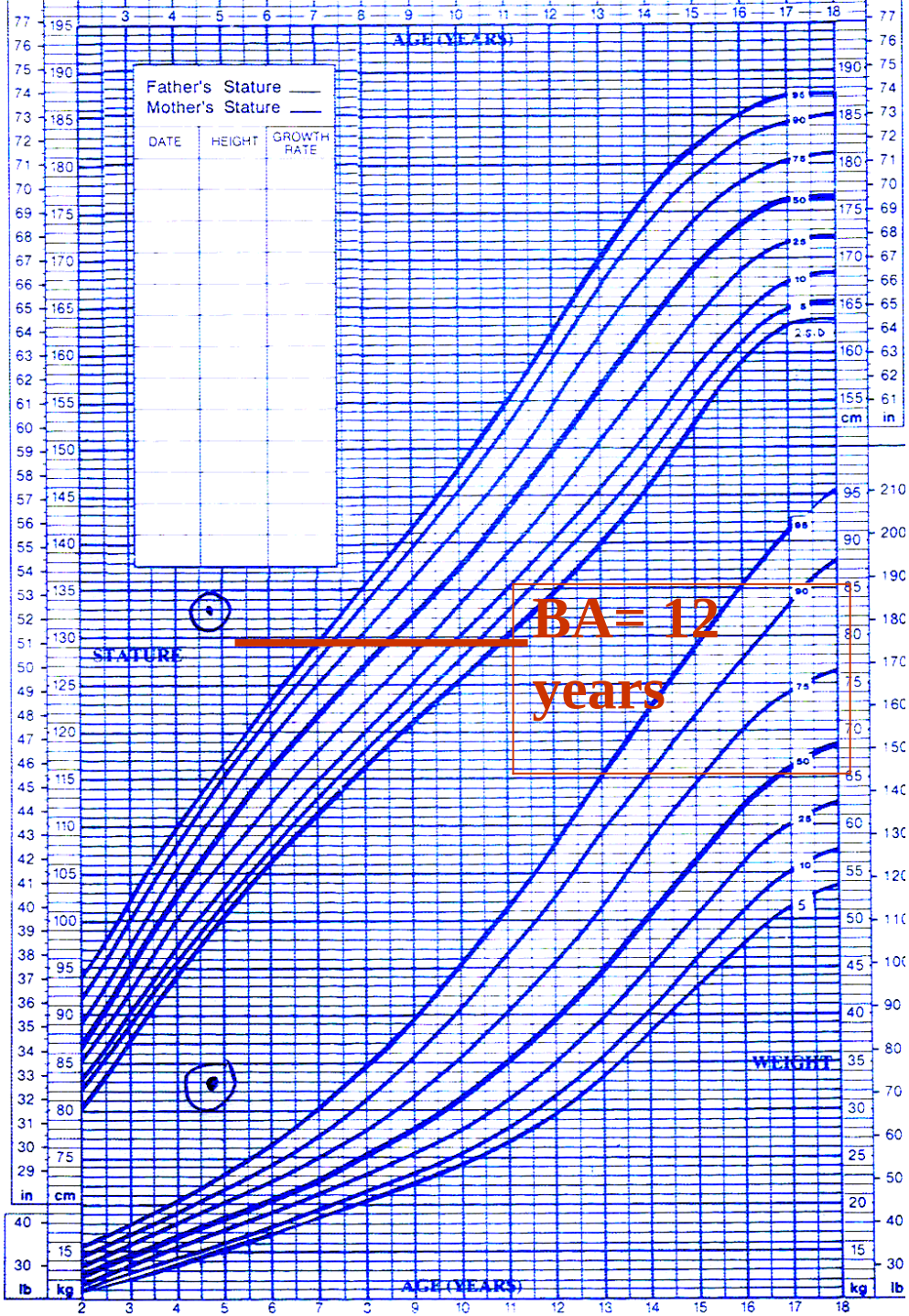
Non – classical form (presentation in childhood / adolescence due to mild or very mild enzyme deficiency)

- Individuals diagnosed with non-classic CAH should be offered treatment when they manifest signs or symptoms of androgen excess.
- Low-dose glucocorticoid therapy 6-8 mg/m2/day may be initiated in children with:
  - precocious pubarche/ adrenarche
  - inappropriately early onset of body hair & odor, accompanied by advanced bone age
- Other common indications for treatment in Adolescents are:
  - hirsutism, oligomenorrhea & acne

In adults:

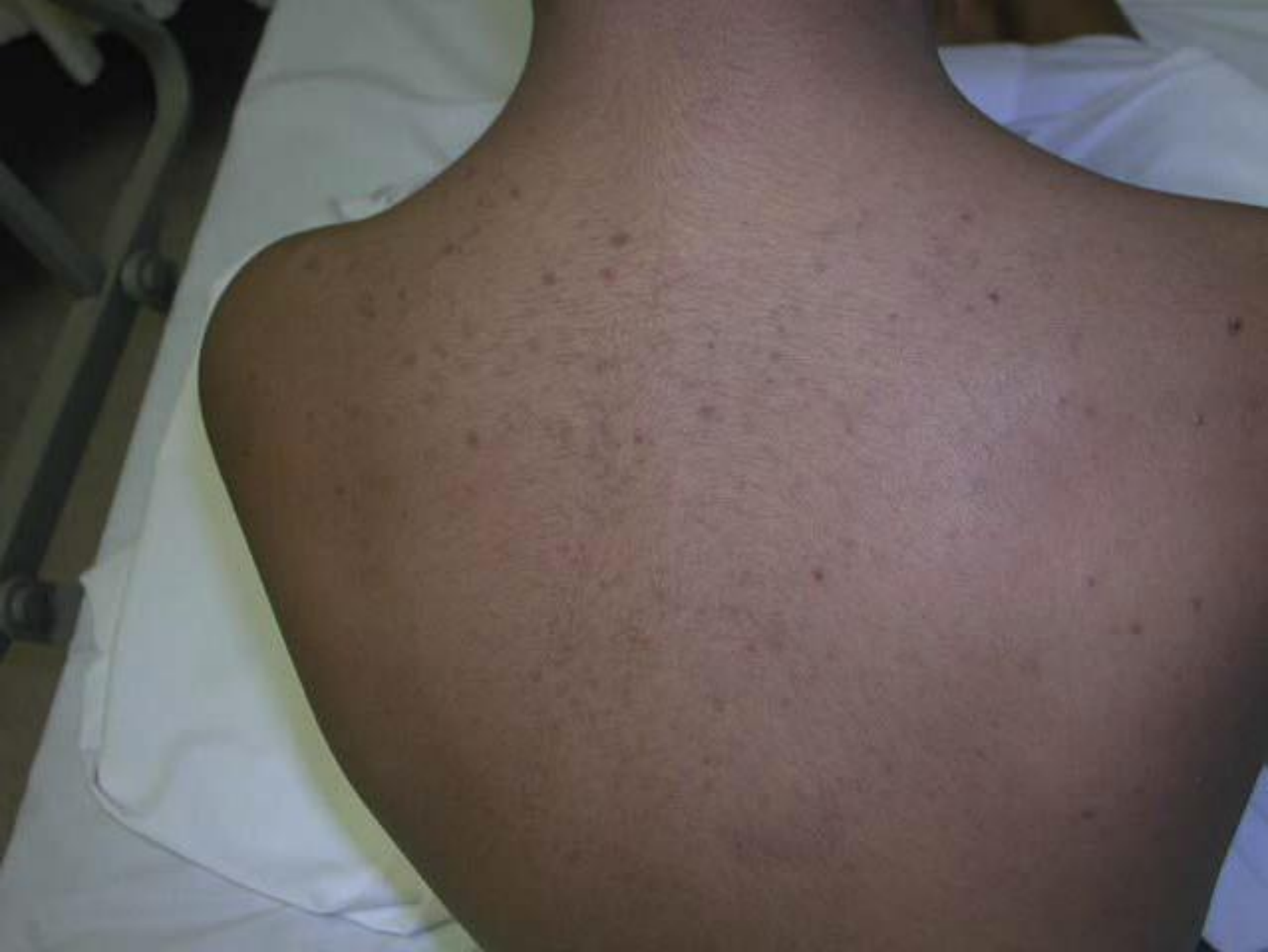
- Infertile female patients diagnosed with non-classic CAH should also be treated, as they may more readily become pregnant if the hormonal imbalance is the principal obstacle to conception
- Men with non-classic CAH may achieve improved sperm counts & fertility with glucocorticoid treatment
- Although rare, testicular enlargement in non-classic males is also an indication for glucocorticoid therapy

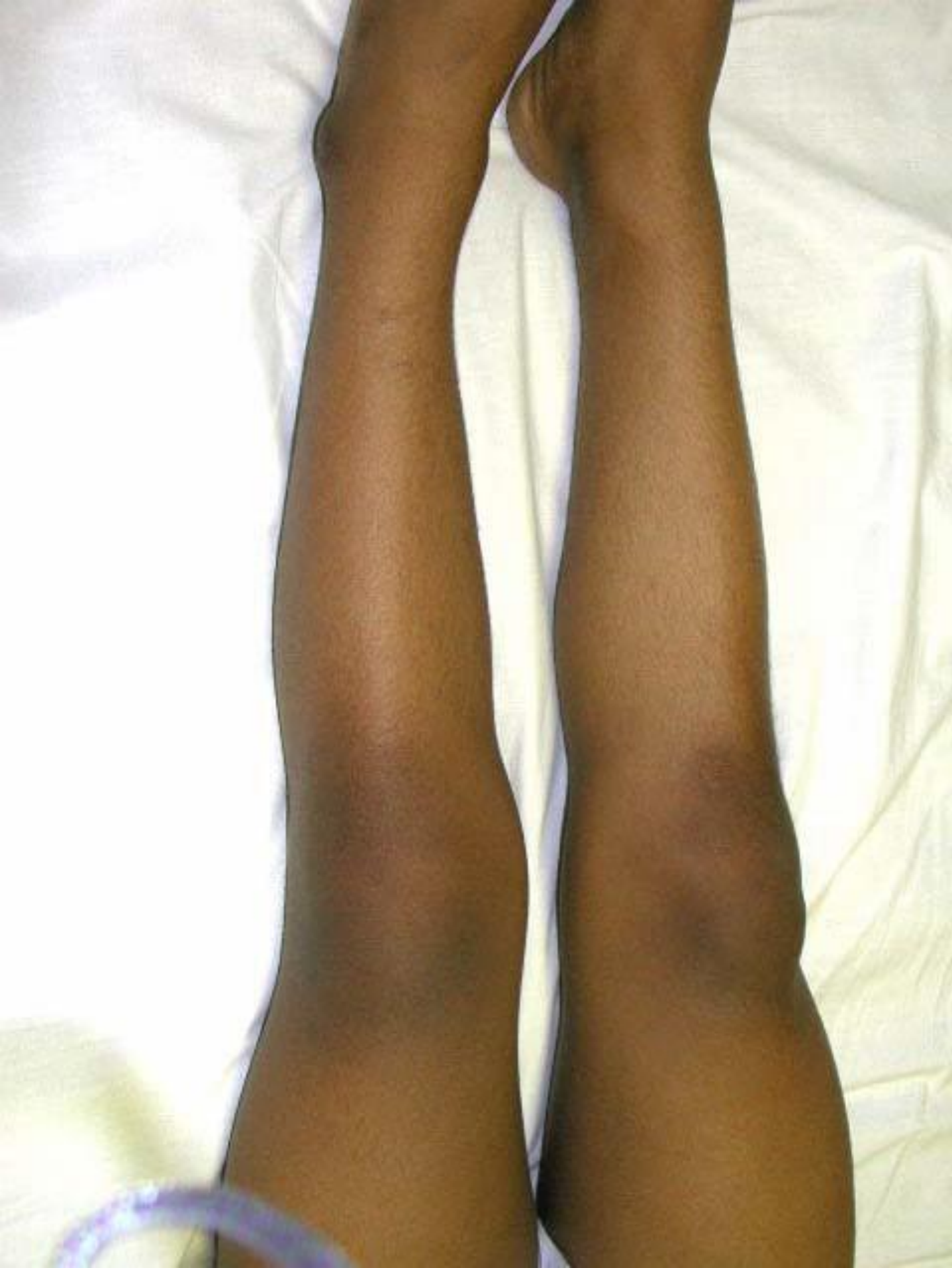

132.8 cm

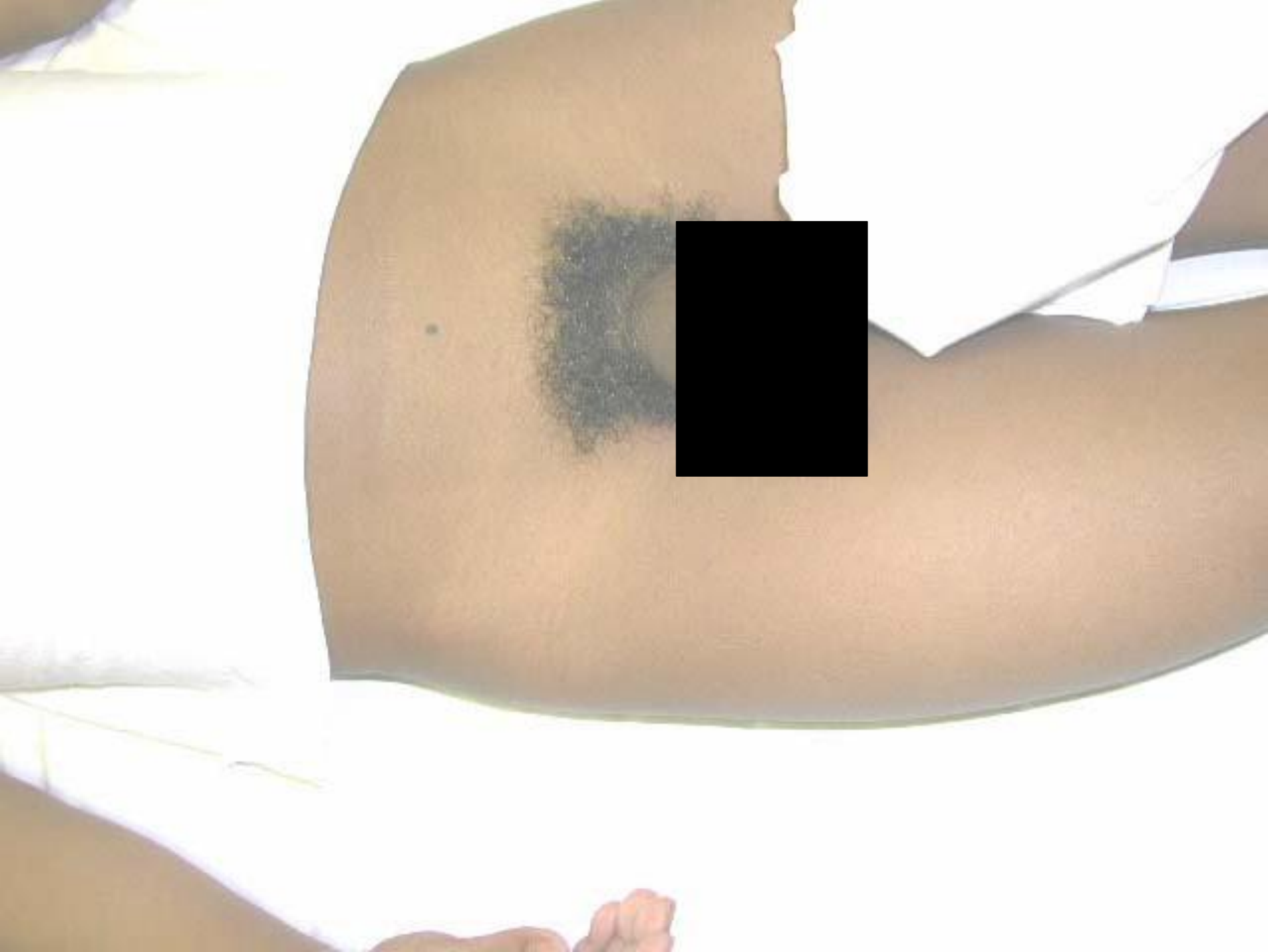


Height = 132.8 cm

Weight = 33 kg







Management of other sexual differentiation disorders

Testosterone Replacement Therapy

Testosterone biosynthesis defects

- Five enzymes needed for conversion of cholesterol to testosterone:

  1)P-450 scc (Lipoid adrenal hyperplasia)

  2)3 β- HSD

  3) P-450 c17

  4) P-450 c17 (17,20 lyase)

  5) 17 β-Hydroxysteroid dehydrogenase

1, 2 & 3 are needed for glucocorticoid synthesis

- Testicular Aplasia / Hypoplasia
- Testicular dysgenesis (incomplete gonadal dysgenesis)
- PAIS
- Testicular vanishing syndrome
- Isolated micropenis

- Intramuscular depot injections of testosterone esters are commonly used in males; another option is oral testosterone & transdermal preparations
- Patients with PAIS may require supraphysiologic doses of testosterone for optimal effect
- Low doses of IM testosterone at 50 mg once a month will bring about some degree of virilization & induce puberty without jeopardizing adult height potential

- Adolescents should be treated with long-acting injectable testosterone at low dose that increases over 18 to 24 months period from 50 mg monthly up to 200 mg q 2 to 4 wk

- Potential adverse effects include fluid retention, acne, occasionally, transient gynecomastia
- Therapy prevents or reduces the risk of osteopenia , vasomotor instability, increases libido & prevents impotence
- Because they carry the risk of hepatocellular dysfunction or tumour formation, oral androgens should not be used

5 α - Reductase deficiency

DIHYDRO TESTOSTERONE (ANDRACTIN)

- Deficiency of 5 α - reductase has been shown to lead to micro penis & hypospadias
- It is unclear in what percentage of hypospadias cases this occurs, but it could be as much as 20%
- Applying dihydrotestosterone cream directly to the phallus bypasses the need for 5 alpha reductase
- Theoretically will promote penile growth without systemic side effects of testosterone injection therapy
- In PAIS applying high concentrations of the cream may overcome this deficiency

- It is desirable to measure testosterone & dihydrotestosterone 3 days following HCG stimulation to determine the ratio of T: DHT
- 5 alpha reductase deficiency if plasma testosterone: dihydrotestosterone ratio >20 following HCG stimulation

Dosage

- The cream to be applied twice / day for 2 months
- One turn of the tube delivers approximately 5 gm that should then be applied locally to the phallic shaft region
- The patient is then to be reassessed with measurement of stretched penile length

Risks

- The risks associated with dihydrotestosterone cream should be small

- The treatment is similar to giving testosterone injections with less systemic side effects of the medications, since it is applied locally as a cream

- Theoretical risk is that the cream may cause a long term down regulation of DHT receptors which may result in initial penile growth spurt with later decrease in the final penile length achieved at puberty

Estrogen Replacement Therapy

- All 46,XY DSD patients who were reared female will require life-long hormone replacement therapy
  - Except cases of 5 -reductase deficiency, 17- ketosteroid reductase deficiency, and PAIS, patients who were reared male
- CAIS after bilateral castration
  - Early castration requires subsequent post-pubertal hormone replacement therapy
- Mixed gonadal dysgenesis with female rearing

- Estrogen deficiency has potent, deleterious effects on the skeleton that can increase risk for stress fracture
- Estrogen deficiency also appears to promote fat accumulation
- There is evidence that hormone replacement attenuates the negative effects of hypogonadism on body composition & bone density which are mediated primarily by estrogens rather than progestins

- Females with Hypogonadism require estrogen supplementation to induce pubertal changes and menses
- Doses:
  - Start low dose of conjugated estrogen (Premarin 0.625 mg) every other day initially at age of 14 to enhance bone growth then increase dose gradually over 2 years time
  - A progestin is usually added after breakthrough bleeding develops or within 6-12 months of continuous estrogen
  - Cycling with Provera (5-10 mg) to induce regular menstruation
  - There is no evidence that the addition of cyclic progesterone is beneficial in women without uterus


Thank you