Two patients with androgen excess

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Symposium stichting Kwaliteitsbewaking Medische Laboratoriumdiagnostiek

9 december 2015

amC Endocrinology & Metabolism

Casus 1

Man, 36 jaar.

vaste relatie, geen kinderen

RvV: Polyglobulinemie bij anabole steroiden gebruik

A/ Afgelopen 10 jaar 5 kuren met anabole steroiden, laatste 3 maanden geleden afgerond.

Kort na laatste kuur hoofdpijn en POB. Bij onderzoek elders verhoogd hematocriet waarvoor enkele malen aderlating.

Nu wat gevoelige tepels en verminderd libido.

Casus 1

Lichamelijk onderzoek

lengte 1.88m, gewicht 88 kg

geen gynaecomastie

huid: geen afwijkingen

lever niet vergroot

genitaal aan de kleine kant, testes L=R, ≈ 6 ml

Casus 1

Laboratorium

Hb 10.4 mmol/L, Ht 0.50 l/l

Kreatinine 82 umol/L, ALAT 10 U/L, ASAT 14 U/L

Endocrinologie:

LH	7 U/L	(1-12)
FSH	12 U/L	(1-12)
E2	69 pmol/L	(<130)
Prolactine	12 ug/L	(<15)
Testosteron	6.4 nmol/L	(9.0-30)
SHBG	48 nmol/L	(14-71)

AAS most often detected

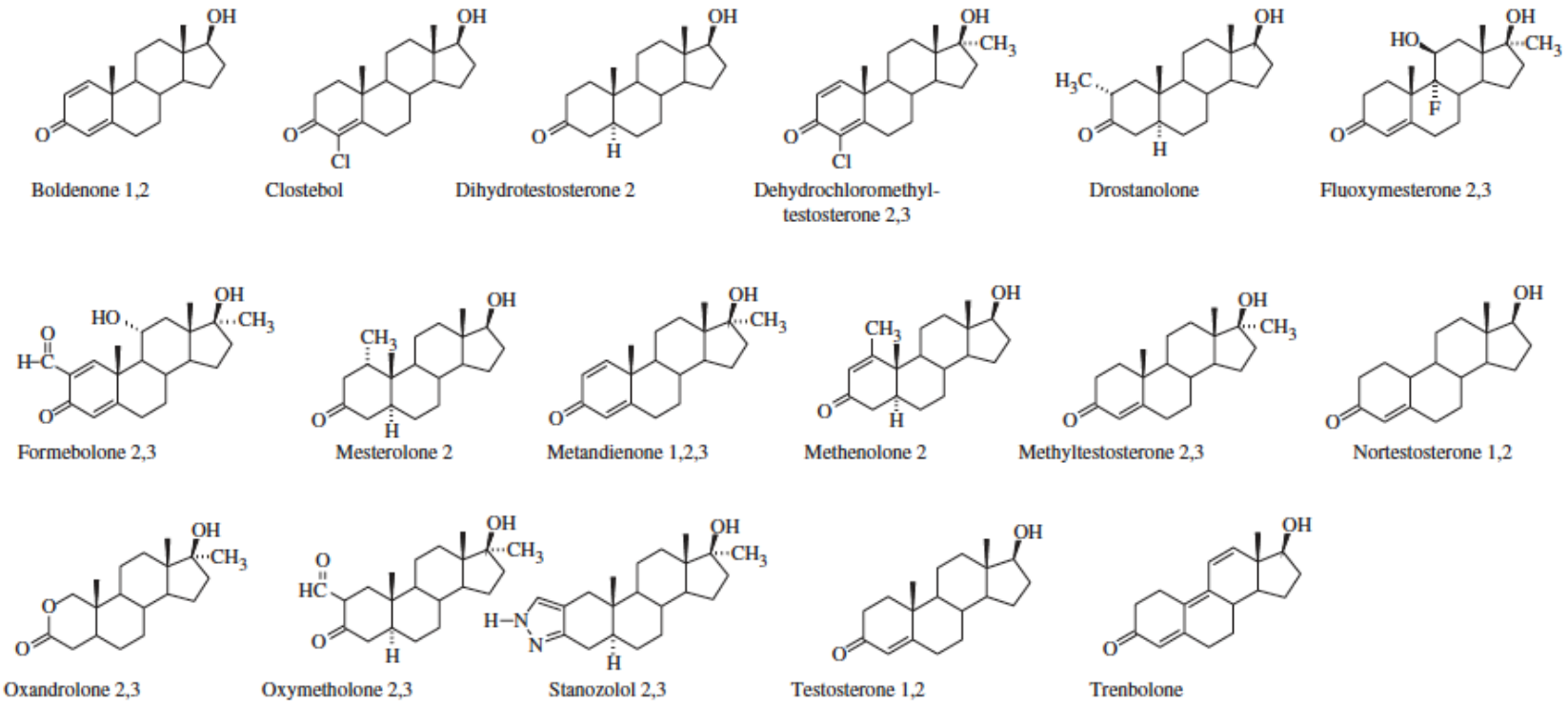


Figure 1

Anabolic androgenic steroids (AASs) detected most often in international doping control tests. 1: AASs that can be aromatised, 2: AAS that are or can be 5α-reduced, 3: AASs with the liver-toxic 17α-alkylation (adapted from (1)).

Niedschlag EJE 2015

AAS preparations and co-ingestion

anabool (merknaam)	dosering therapeutisch	praktijk ♂	praktijk ♀
oraal*			
oxymetholon (Anadrol)	tot 150	25-150	n.a.
oxandrolon (Anavar/Oxandrin)	2,5-20	15-25	5-10
methandrostenolon (Dianabol)	5	20-50	5
stanozolol (Winstrol/Stromba)	6	15-40	5-10
danazol (Danatrol)†		100-800	100-800
testosteron-undecanoaat-ester (Andriol)†	40-120	240-480	n.a.
methenolon (Primobolan)	100-150	50-150	50-75
mesterolon (Proviron)†	25-75	50-150	25
injectie‡			
nandrolon (Deca-Durabolin/ Laurabolin)†	max. 200	200-600	50
boldenon (Equipoise/Ganabol)	uitsluitend veterinair	200-400	50-75
methenolon (Primobolan)	100	200-600	50-100
trenbolon (Parabolan/Finaplix/ Finajet)	75 mg/10 dagen	150-350	n.a.
testosteron (Sustanon/ Omnadren/Testoviron)†	100 of 250 mg/ 2 of 3 weken	200-1000	n.a.
stanozolol (Winstrol)	50 mg/2-3 weken	150-350	0-50

"Stacking" "Cycling" "Pyramiding"

Enquete onder AAS gebruikers (n=500)
96% gebruikt ook andere middelen:

Hormonen

Schildklierhormoon	46%
Groeihormoon	26%
Insuline	25%
IGF-1	10%

Stimulantia en gewichts-reductie

Efedrine	68%
Cafeine	63%
Clenbuterol	58%
Yohimbine	29%

Maskeren, tegengaan bijwerkingen

Clomifeen	59%
Aromataseremmers	59%
Tamoxifen	53%
Choriongonadotrofine	39%
Diuretica	10%

Woerdeman et al. NTvG 2010

Bijwerking AAS

♀
hirsutisme
stemverlaging
beharing volgens mannelijk patroon
clitoris-hypertrofie
menstruatiestoornissen
involutie van borstklierweefsel

♂
infertiliteit
gynaecomastie
versterking van het libido
testisatrofie
priapisme
prostaathyperplasie

cardiovasculair systeem
verminderde hartfunctie
verlaging van hdl-cholesterol
verhoging van ldl-cholesterol
verhoging van Hb en hematocriet

lever
verhoogde waarde leverenzymen
cholestase
levertumoren
toxische hepatitis
peliosis hepatis

huid
acne
striae
oedeem

slaapproblemen
slaapapneu

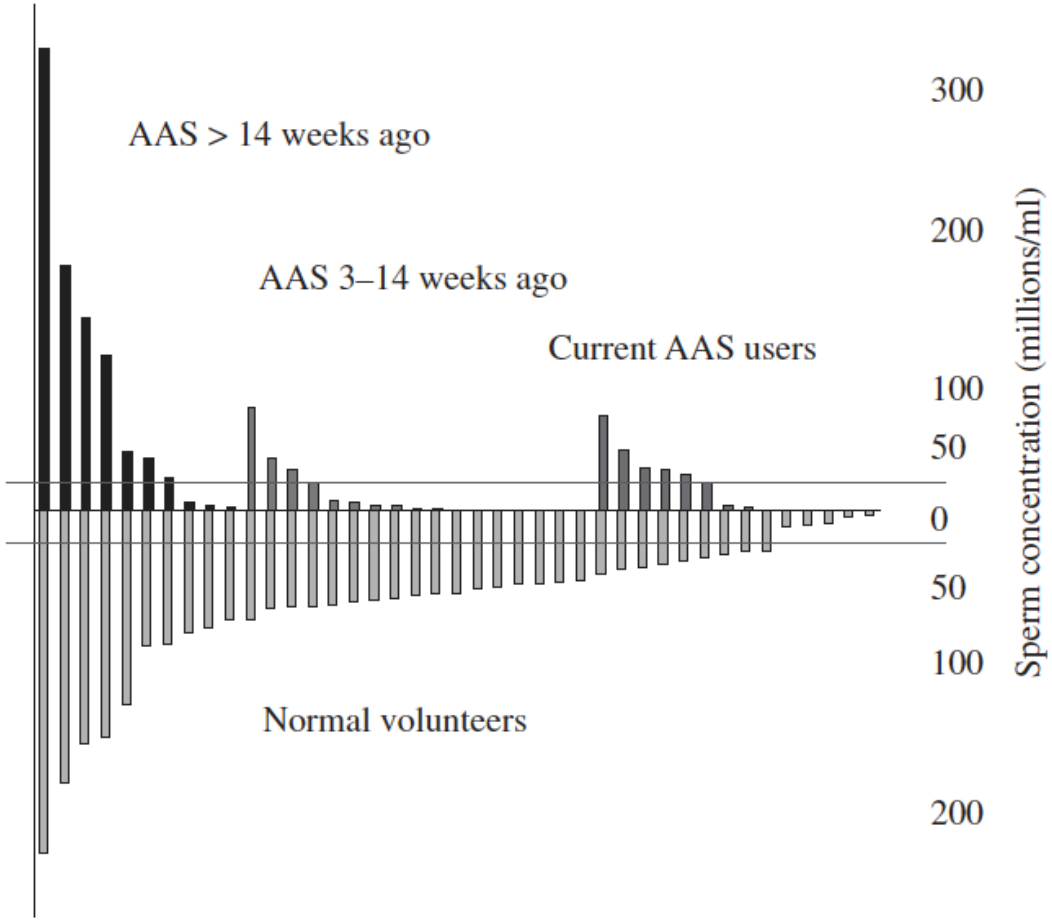
psychiatrische en gedragsproblemen
agressief en gewelddadig gedrag
hypomanie
stemmingswisselingen
psychose
afhankelijkheid van anabole androgene steroïden
depressie
suïcidaliteit

ten gevolge van de injectie
infectie (hiv, hepatitis B en C)
abcessen
septische artritis

Woerdeman et al. NTvG 2010

Fertility after use of AAS

Bodybuilders n=41, gebruik AAS self-reported



Knuth et al. Fertil Steril 1989

Anabole Androgene Steroiden (AAS)

- Reversibele onderdrukking van de HHG-as met als gevolg subfertiliteit is een uniform verschijnsel tijdens en na het gebruik van AAS
- Het karakteristieke beeld bestaat uit hypogonadotroop hypogonadisme met daarbij enige verkleining en verweking van de testes
- De mate van suppressie hangt af van de dosis, de duur en het type middel (aromatiseerbaar *vs* niet-aromatiseerbaar)
- De duur van suppressie hangt af van de cumulatieve dosering, de aard en toedieningsvorm van het gebruikte middel (of combinatie van middelen)
- 3 maanden suppressie na de laatste toediening is heel gebruikelijk

Niedschlag EJE 2015

Casus 1

Vervolg:

Patiënt uit kinderwens met zijn partner

Semenanalyse: azoospermie

Testes volume (4-8 ml bdz) geduid als te laag om te verklaren door intermitterend AAS gebruik

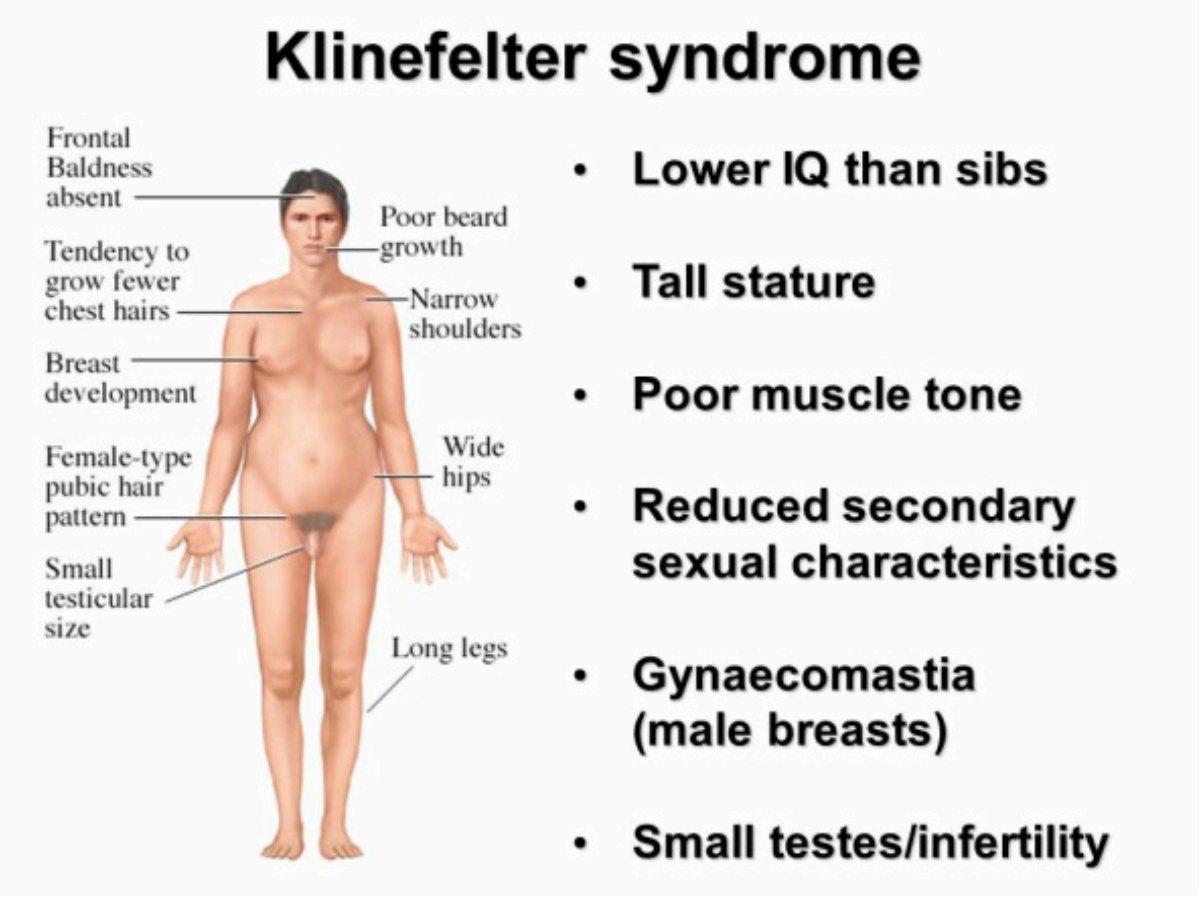
Vervolgonderzoek ingezet..

Casus 1

Karyotpering: *XXY*

Diagnose: Klinefelter syndroom

Behandeling?



Casus 2

Vrouw, 24 jaar, Hindoestaans-Surinaams

vaste relatie, geen kinderen

RvV: overmatige beharing, menstruatie stoornissen

VG: blanco

A: Sinds 1 jaar langzaam onstane diffuus overmatige beharing

Zelf al veel maatregelen genomen; scheren, epileren. Komt snel terug.

Menstruaties sinds stoppen OAC >1 jaar geleden onregelmatig.

Menarche 13 jaar, normale puberteitsontwikkeling.

op termijn kinderwens

Medicatie: Finasteride 5 mg 1dd sinds 2 mnd (huisarts) , weinig effect

Casus 2

Lichamelijk onderzoek

lengte 1.65m, gewicht 88 kg, BMI 31.2 kg/m^2

Obees, centripetale vetverdeling, milde buffalo hump

huid: *acne vulgaris* gelaat en borst, geen striae of hematomen

lever niet vergroot

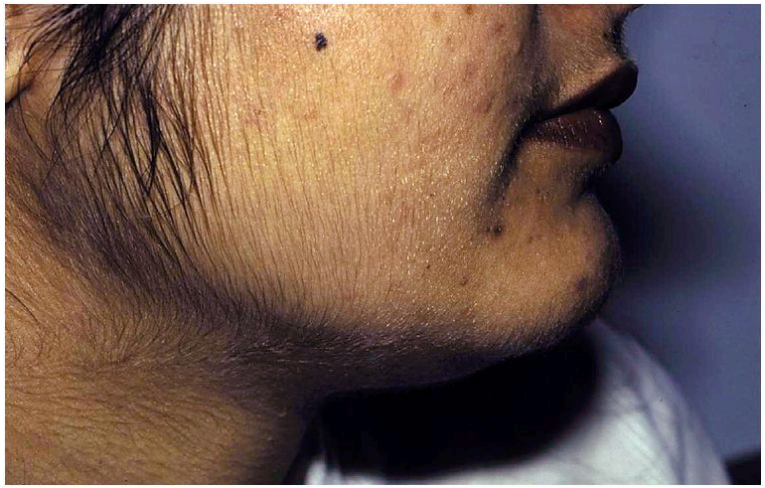
genitaal: geen clitoromegalie

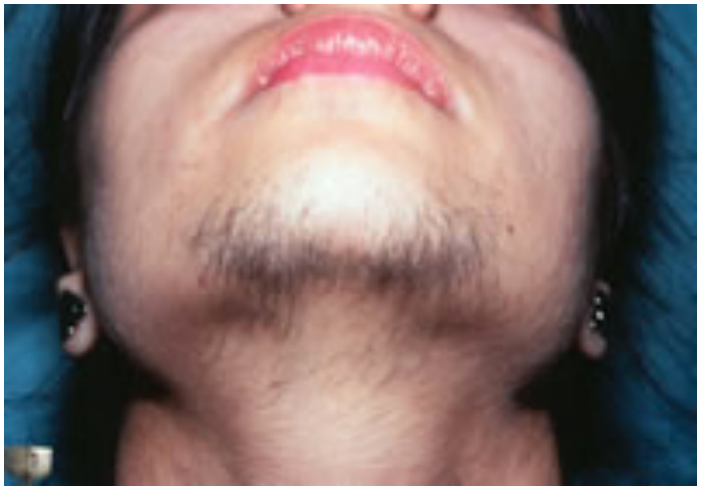
beharing: toegenomen in gelaat, borst, buik, rug, ledematen en schaamstreek

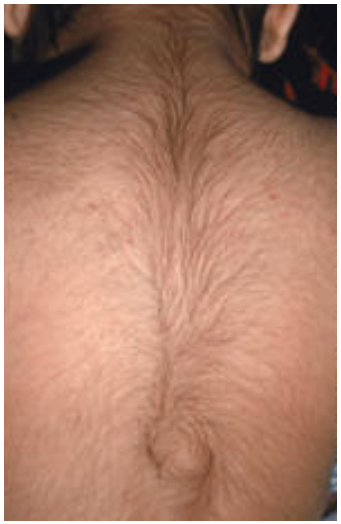
TVE elders: normaal aspect en grootte van adnexen

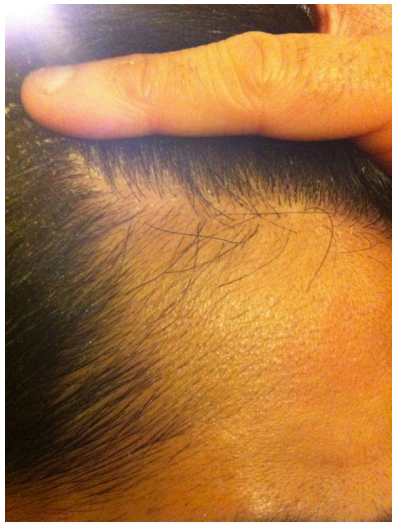
Casus 2

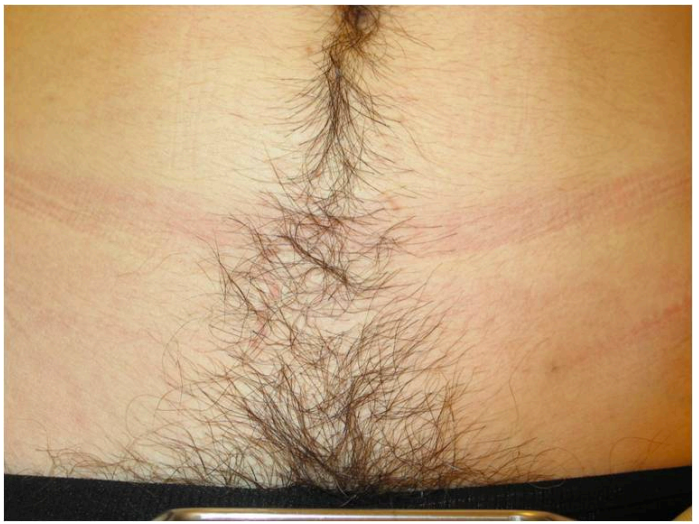
Lichamelijk onderzoek



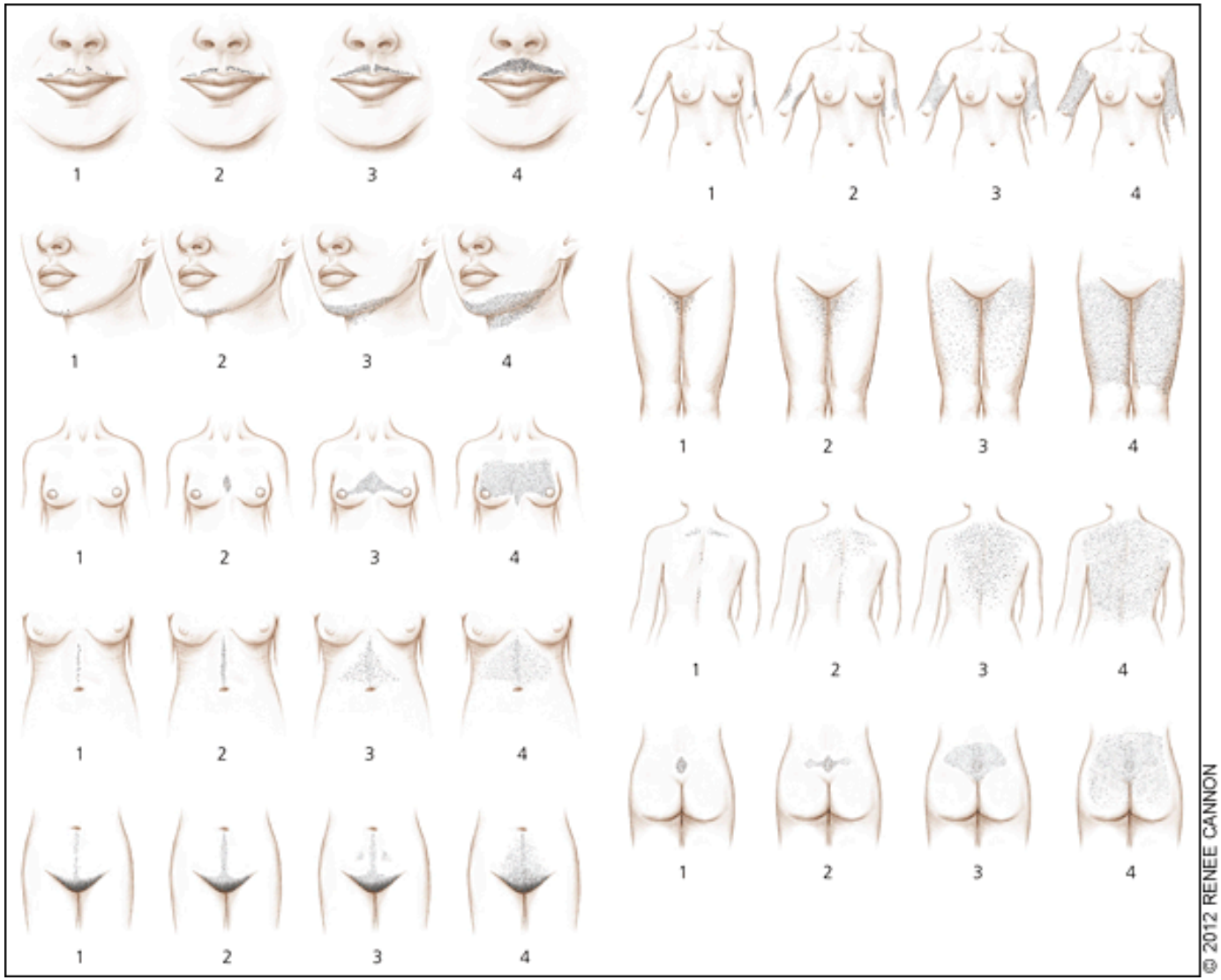








Ferriman-Gellway hirsutism scale



<8	normal
8-15	mild
>15	moderate-severe

Casus 2

Laboratorium

LH	3 U/L	(1-12)
FSH	8 U/L	(1-12)
E2	530 pmol/L	
Prolactine	18 µg/L	(<20)
Testosteron	3.4 nmol/L	(0.3-1.6)
Androstenedion	35 nmol/L	(0.1-5.4)
DHEAS	19 µmol/L	(1-12)
17-OH progesteron	156 nmol/L	(0.6-3.3)

Dexamethason 1 mg suppressietest: cortisol <50 nmol/L

24-uurs cortisolurie 120 nmol/24u

Androgen excess in females: causes

Principal causes of androgen excess in females of reproductive age:

Ovarian
Polycystic ovary syndrome (PCOS)
Ovarian tumor (Sertoli-Leydig cell tumor)

Adrenal
Nonclassic Congenital Adrenal Hyperplasia (NCCAH)
Cushing's syndrome
Adrenal tumor (adenoma, carcinoma)

Other
Hyperprolactinemia, hypothyroidism
Medication
Idiopathic hirsutism
Idiopathic hyperandrogenism

TABLE 1. Prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism

	No. of patients	% of total no. of patients
Classic PCOS	538	56.6
Ovulatory PCOS	147	15.5
Idiopathic hyperandrogenism	150	15.8
Idiopathic hirsutism	72	7.6
NCAH	41	4.3
Androgen-secreting tumors	2	0.2

Williams Endocrinology 12th edit, Carmina et al. JCEM 2006

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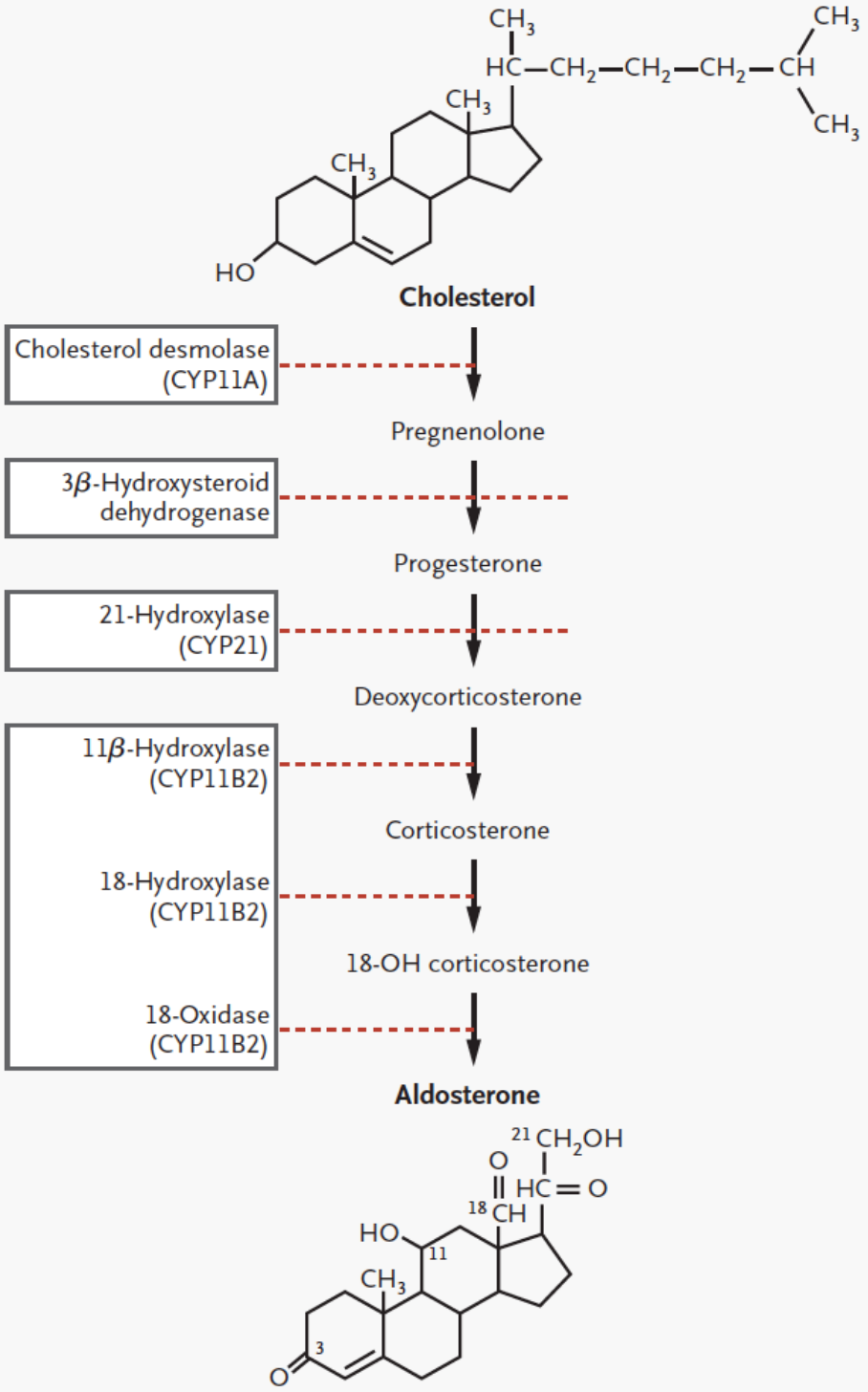
Adrenal steroid biogenesis



Speiser et al, NEJM 2003

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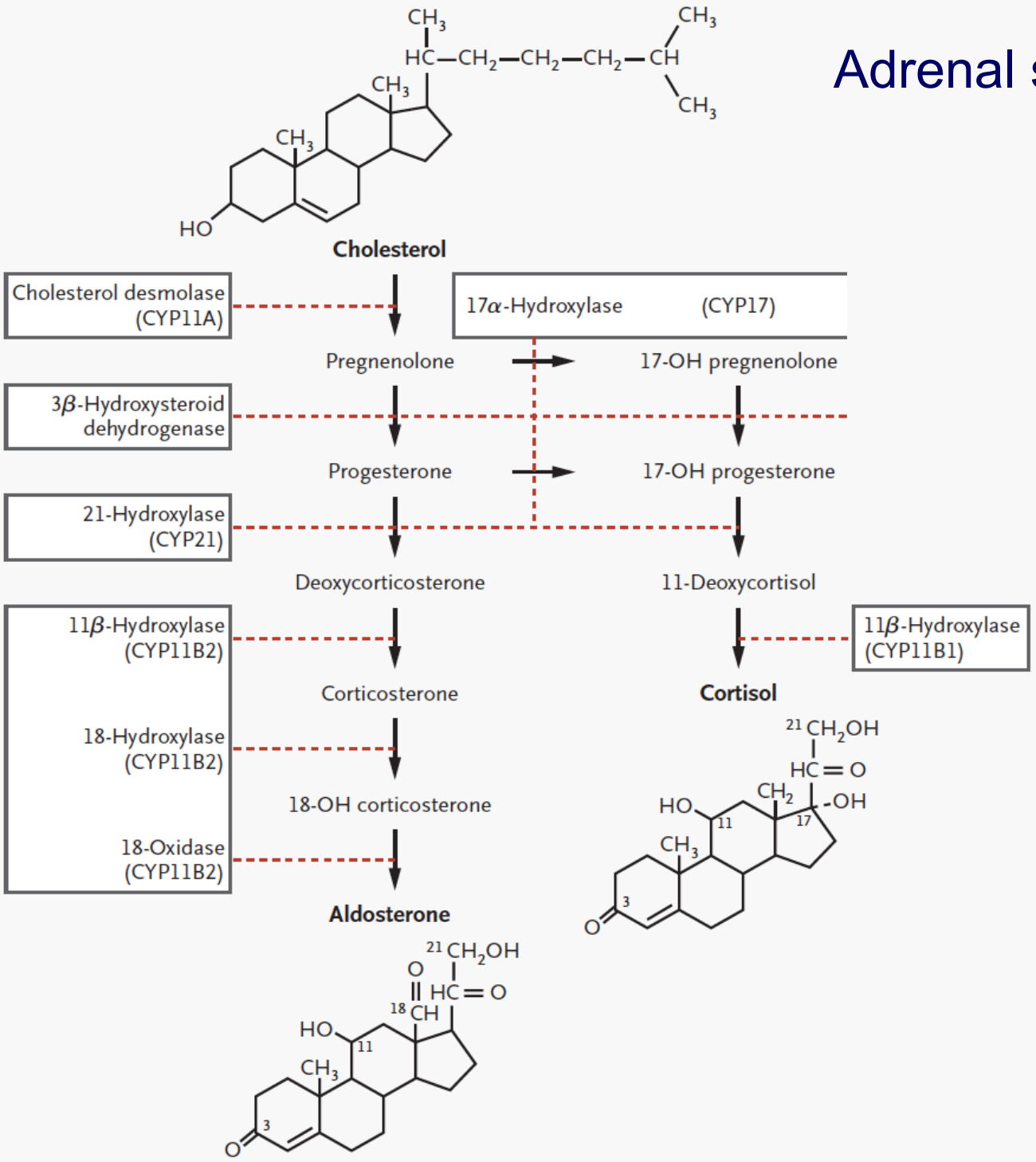

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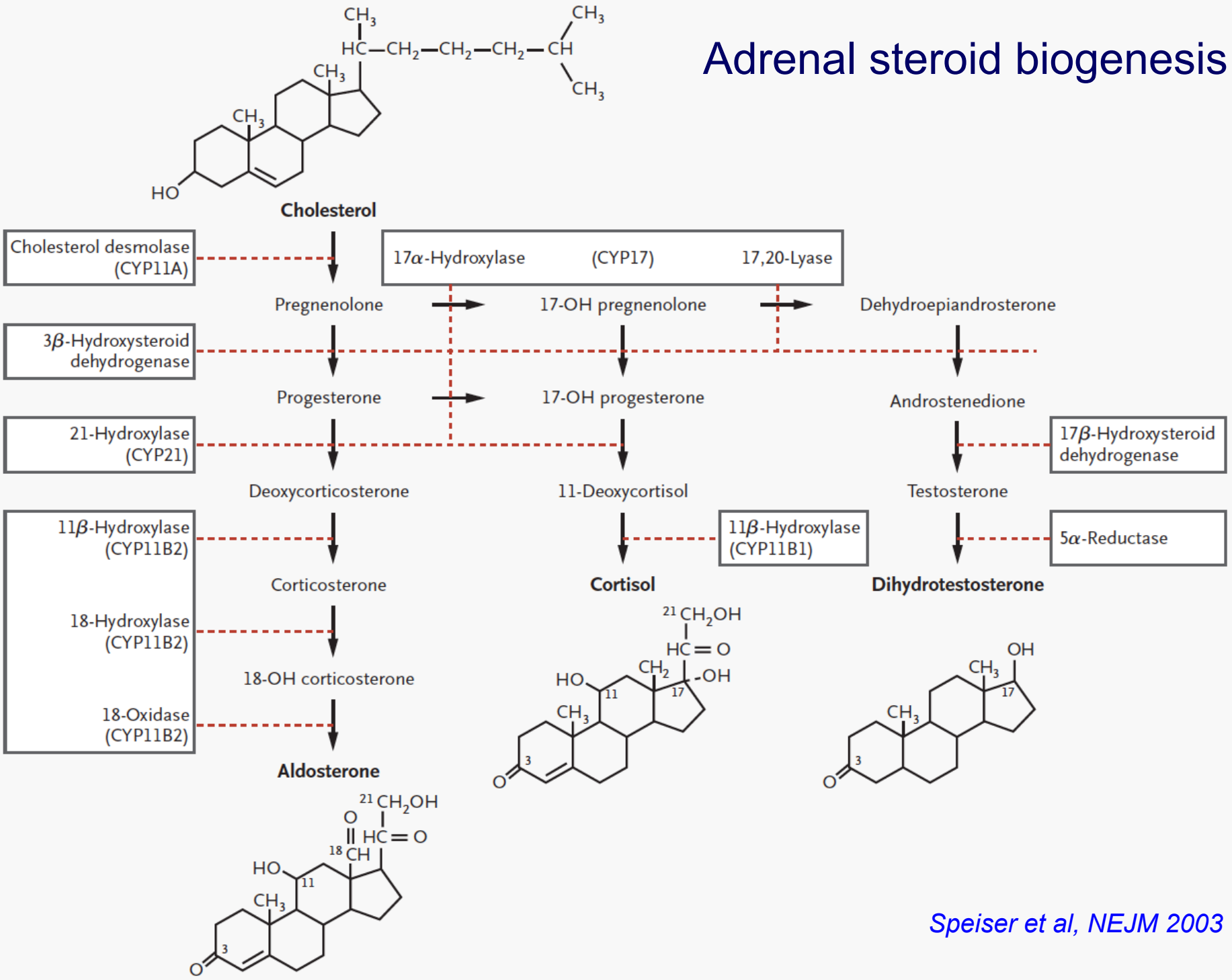

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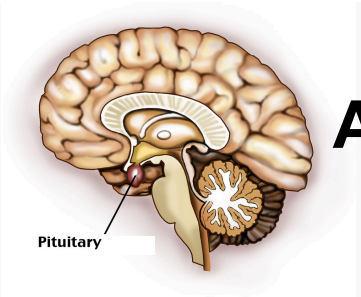
Adrenal steroid biogenesis
in 21-OHD deficiency



ACTH

Cholesterol

Cholesterol desmolase (CYP11A)

Pregnenolone

17α-Hydroxylase (CYP17) 17,20-Lyase

17-OH pregnenolone

Dehydroepiandrosterone

3β-Hydroxysteroid dehydrogenase

Progesterone

17-OH progesterone

Androstenedione

21-Hydroxylase (CYP21)

17β-Hydroxysteroid dehydrogenase

Deoxycorticosterone

11-Deoxycortisol

Testosterone

11β-Hydroxylase (CYP11B2)

11β-Hydroxylase (CYP11B1)

5α-Reductase

Corticosterone

Cortisol

Dihydrotestosterone

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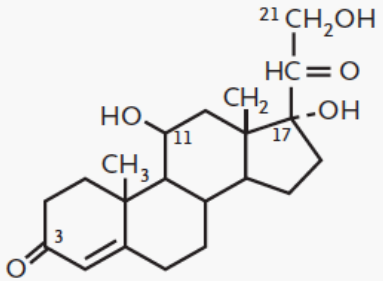
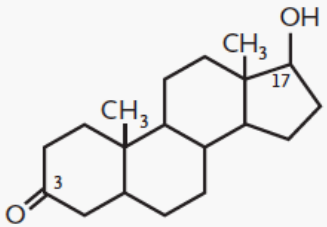
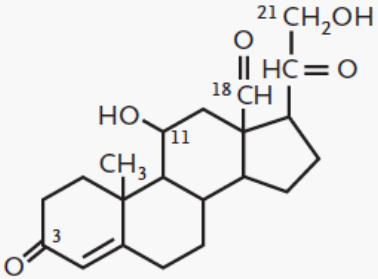
18-OH corticosterone

18-Oxidase (CYP11B2)

Aldosterone







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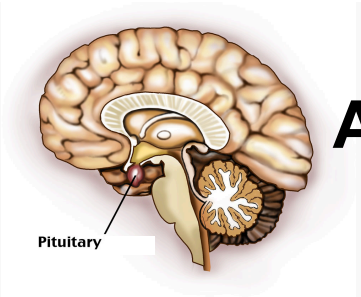

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18-OH corticosterone

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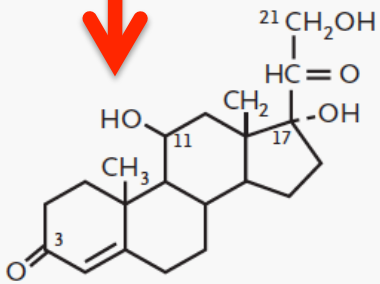

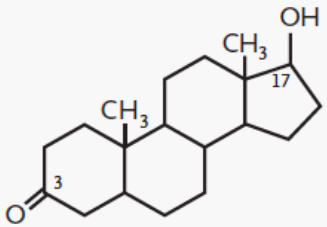

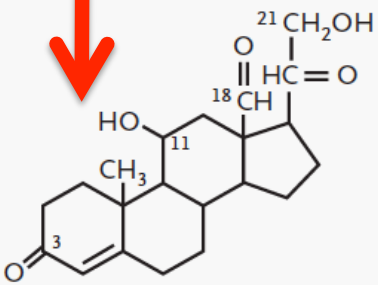

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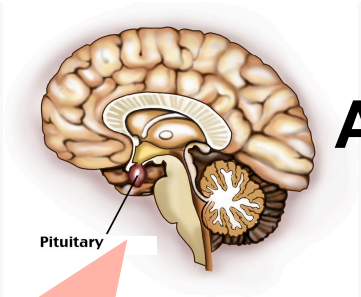

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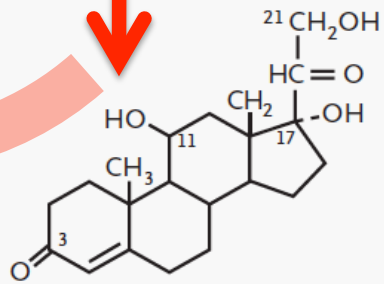

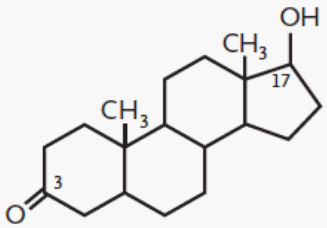

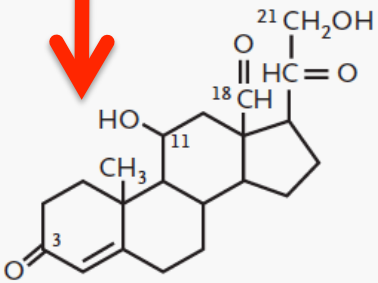

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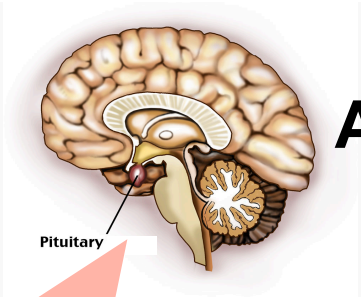

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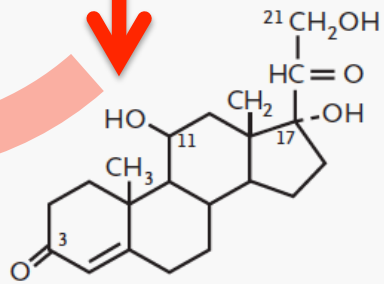

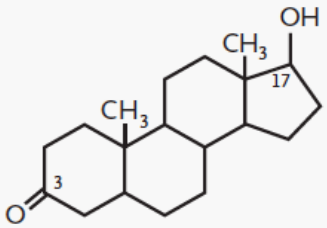

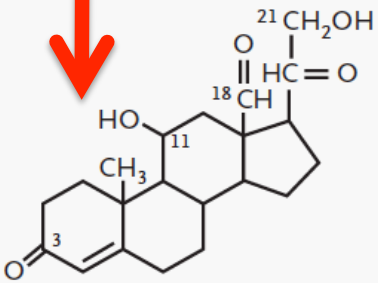

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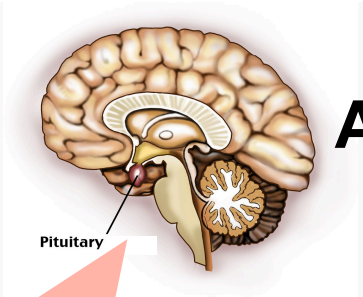

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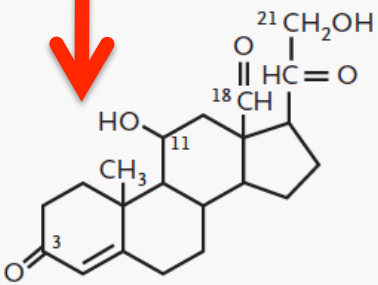
Aldosterone



17α-Hydroxylase (CYP17) 17,20-Lyase

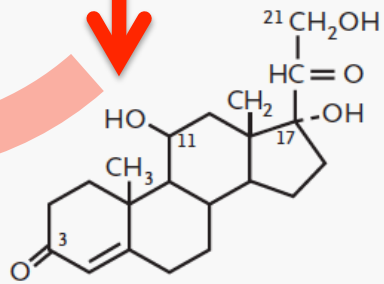
17-OH pregnenolone

17-OH progesterone

11-Deoxycortisol

11β-Hydroxylase (CYP11B1)

Cortisol



Dehydroepiandrosterone

Androstenedione

17β-Hydroxysteroid dehydrogenase

Testosterone

5α-Reductase

Dihydrotestosterone

Androgen excess

Speiser et al, NEJM 2003

Congenital Adrenal Hyperplasia (CAH)

Among the most common inborn endocrine disorders

90-95% caused by 21-hydroxylase deficiency (21-OHD)

Classical CAH, incidence 1: 15000

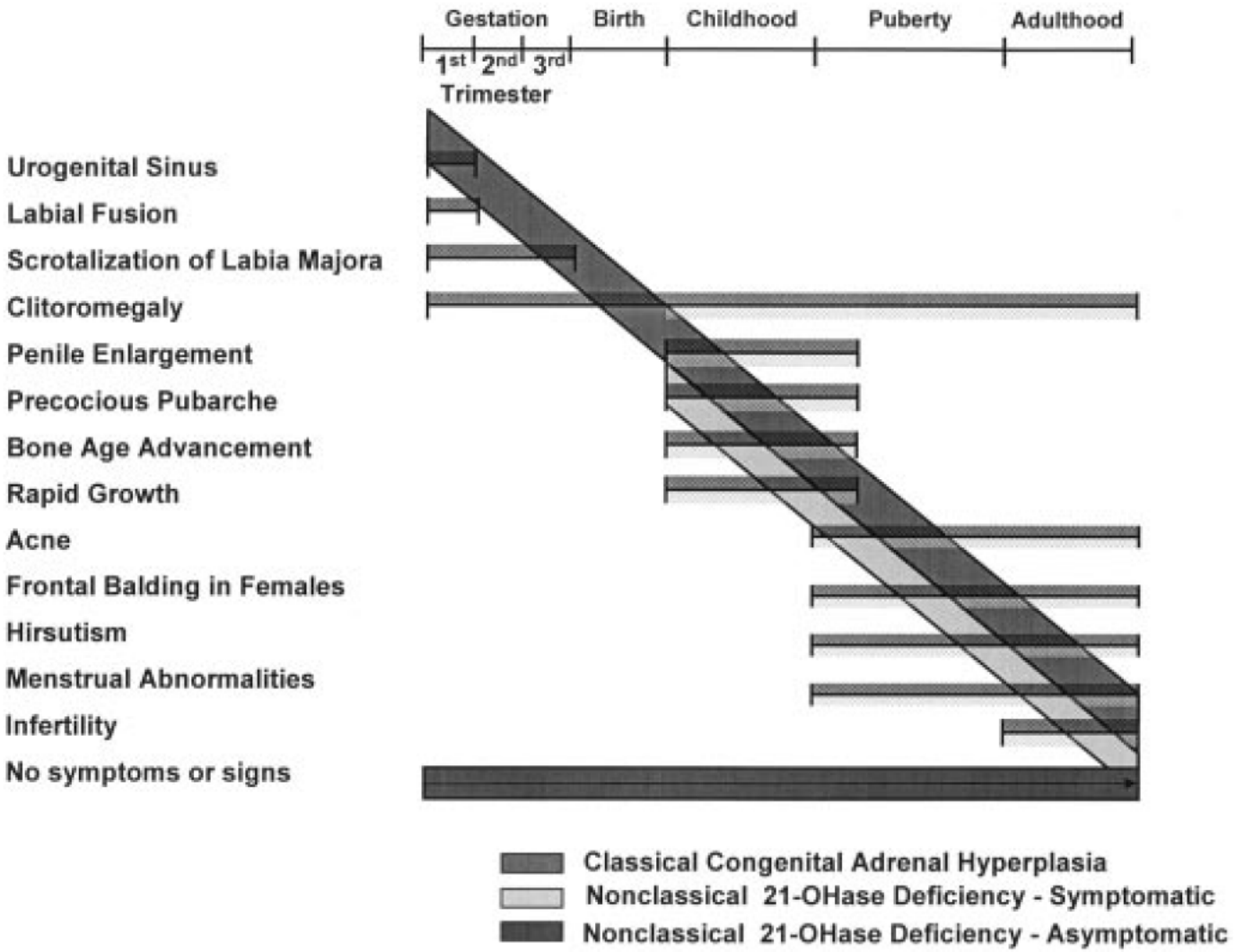
- Salt wasting (75%, aldosterone ↓ , cortisol ↓ , androgens ↑)
- Simple virilising (25%, aldosterone = , cortisol ↓ , androgens ↑)

Non-classical CAH, incidence 1:600 (aldosterone = , cortisol =, androgens =/↑)

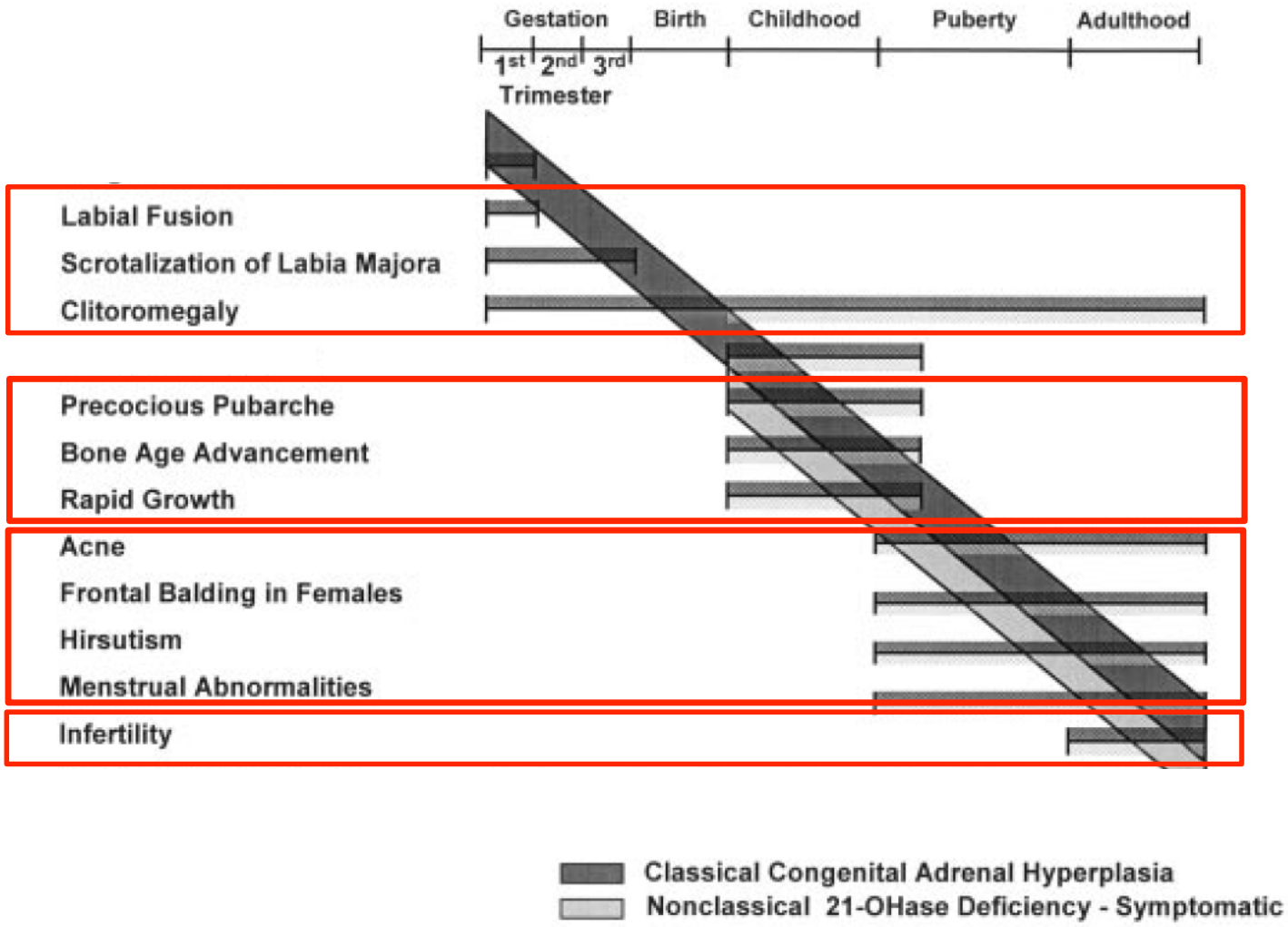
Autosomal recessive inheritance

Not a single clinical entity, rather a spectrum of disease

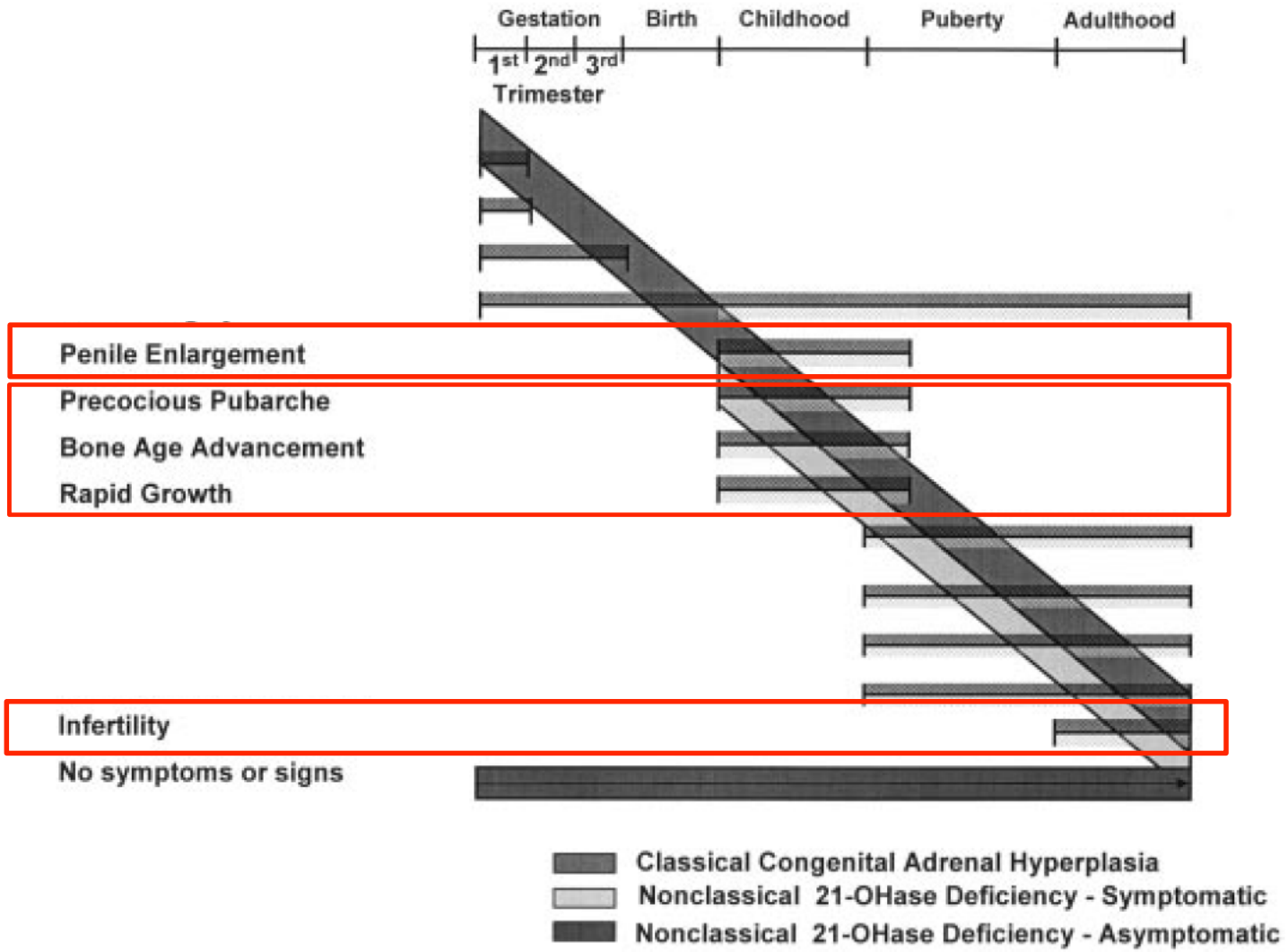
CAH: spectrum of disease



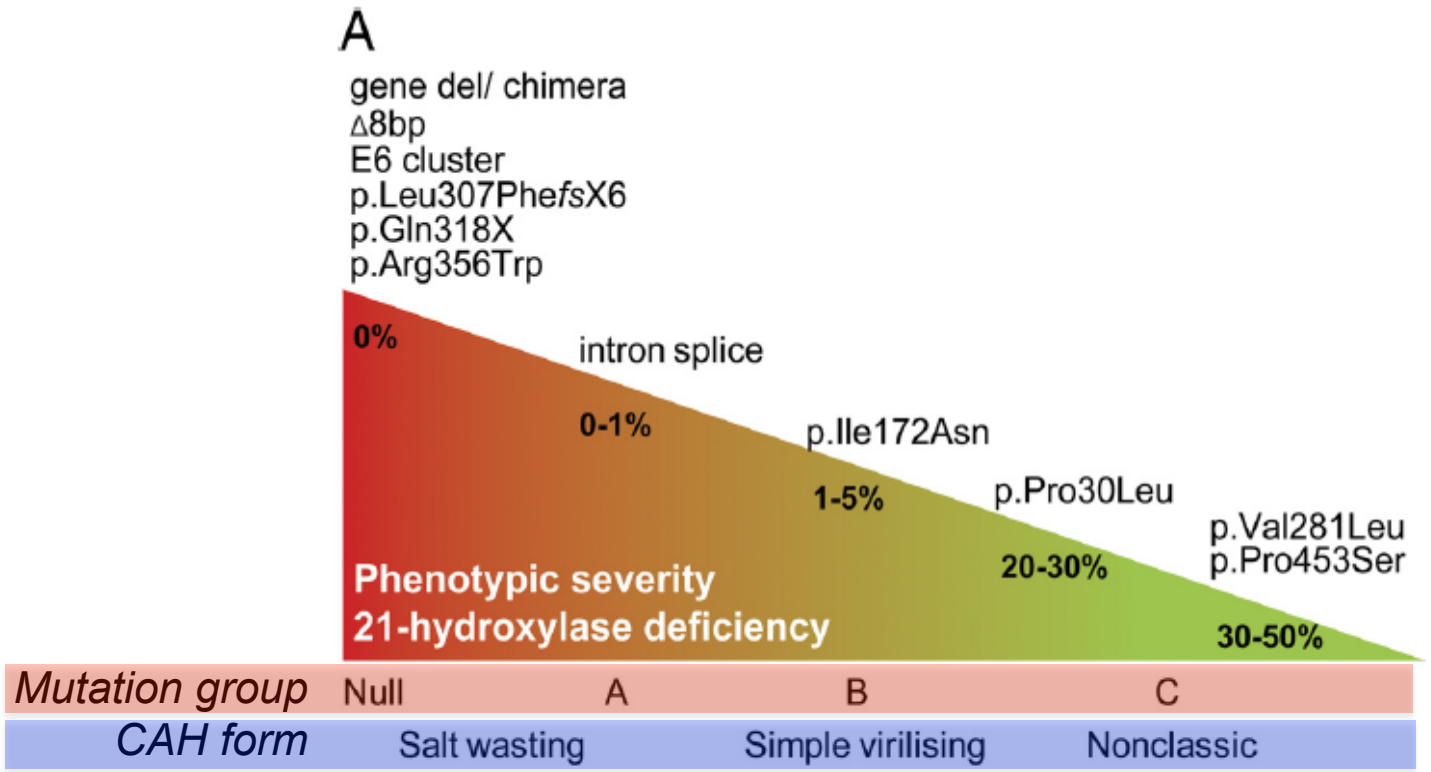
CAH: spectrum of disease in *Females*



CAH: spectrum of disease in *Males*



CYP21A2 genotype-phenotype correlation



Krone JCEM 2013

Diagnostic strategy

Classic CAH: newborn screening ("hielprik") day 4-7 post-partum

17-OH Progesterone introduced in july 2000 (NL)

Non-classic CAH:

1. Screening: 17-OH Progesterone (early morning, follicular phase)

   17-OHP < 6 nmol/L: 21-OHD unlikely

   pittfalls: late afternoon > false negatives, luteal phase > false positives

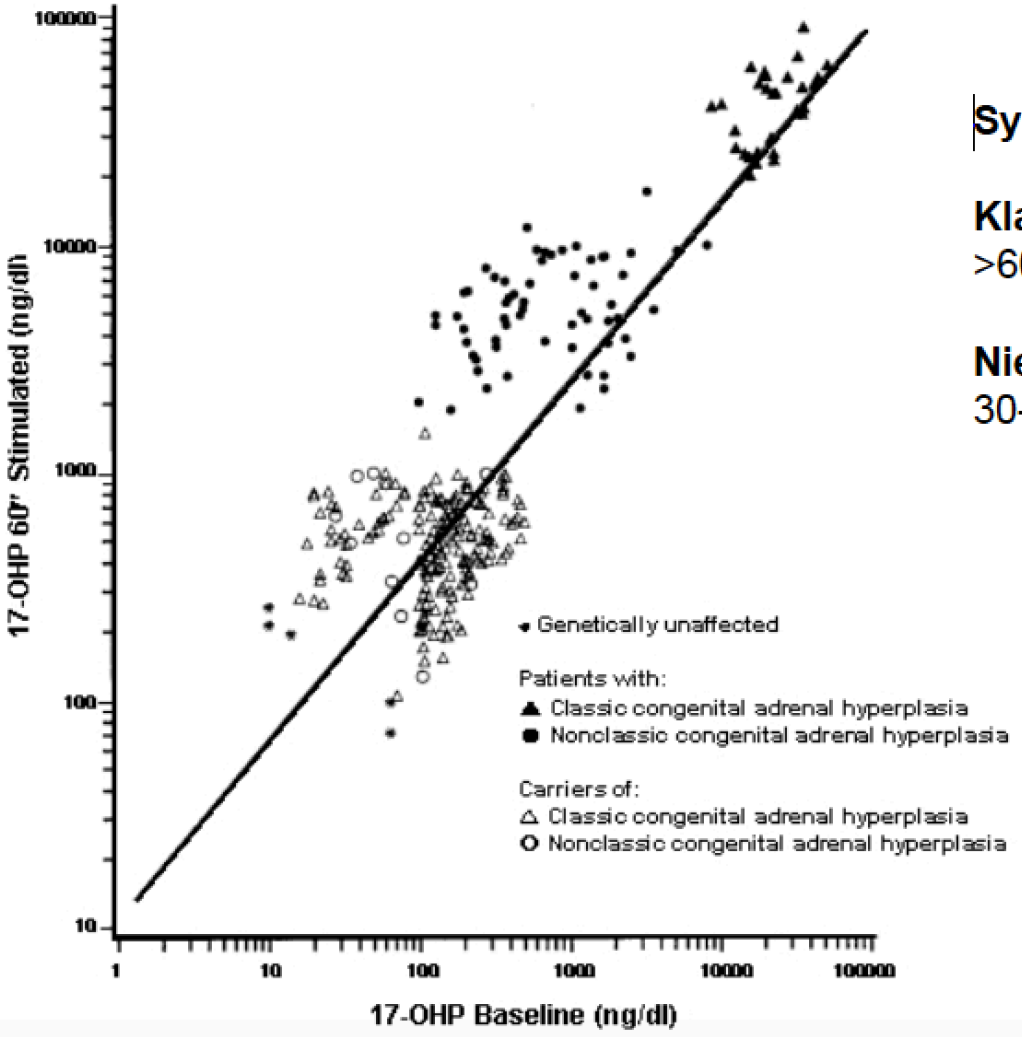
2. Synacthen test (250 µg) measuring 17-OHP after 60 min

   17-OHP >600 nmol/L — classic 21-OHD

   17-OHP 30-450 nmol/L — non-classic 21-OHD

3. $CYP_{21}A_2$ mutation analysis

Synacthen test (17-OHP)



Synacthentest (60')

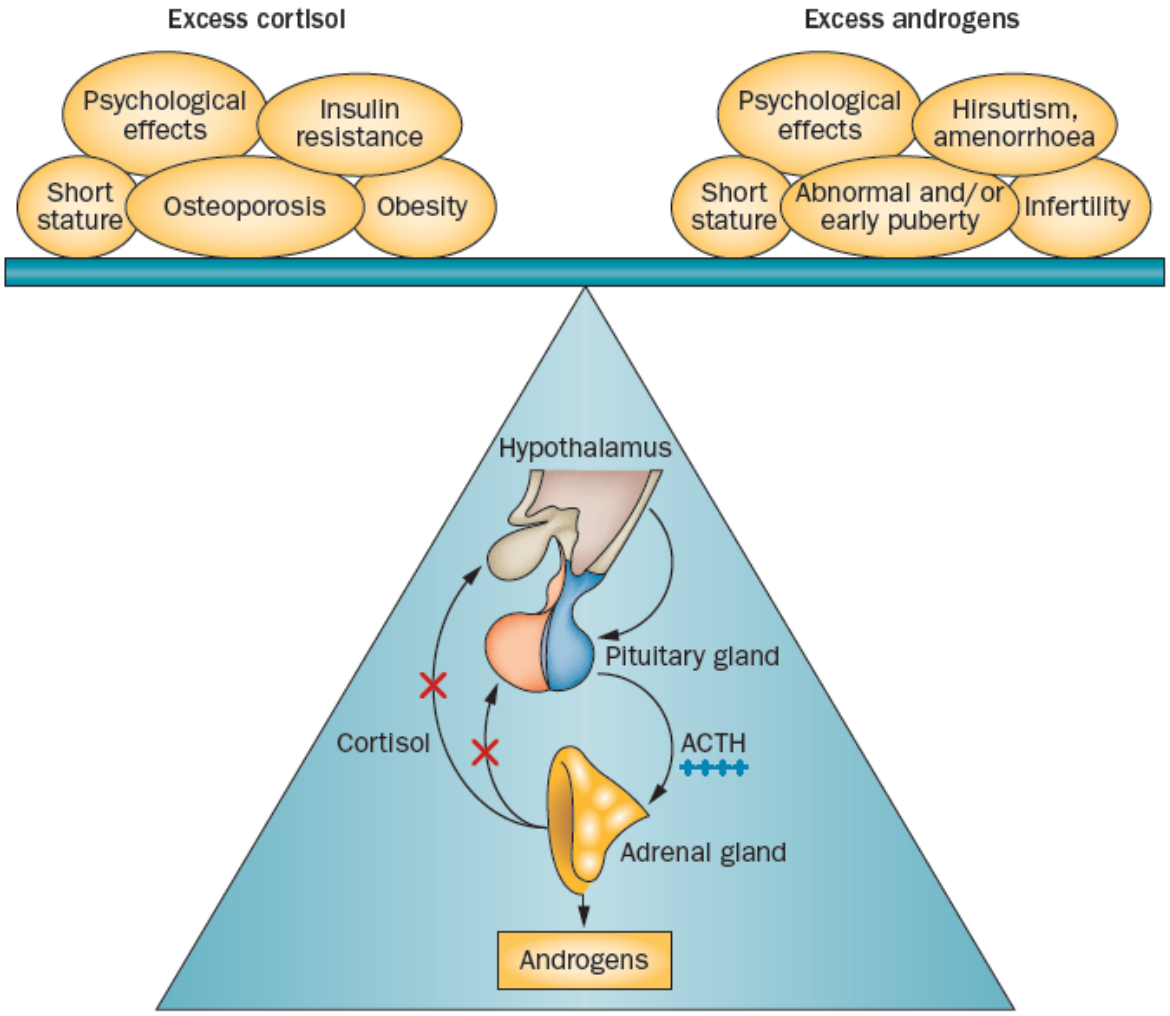
Klassieke 21-OHD AGS
>600 nmol/l

Niet-klassieke 21-OHD AGS
30-450 nmol/l

NCCAH: Treatment goals in females

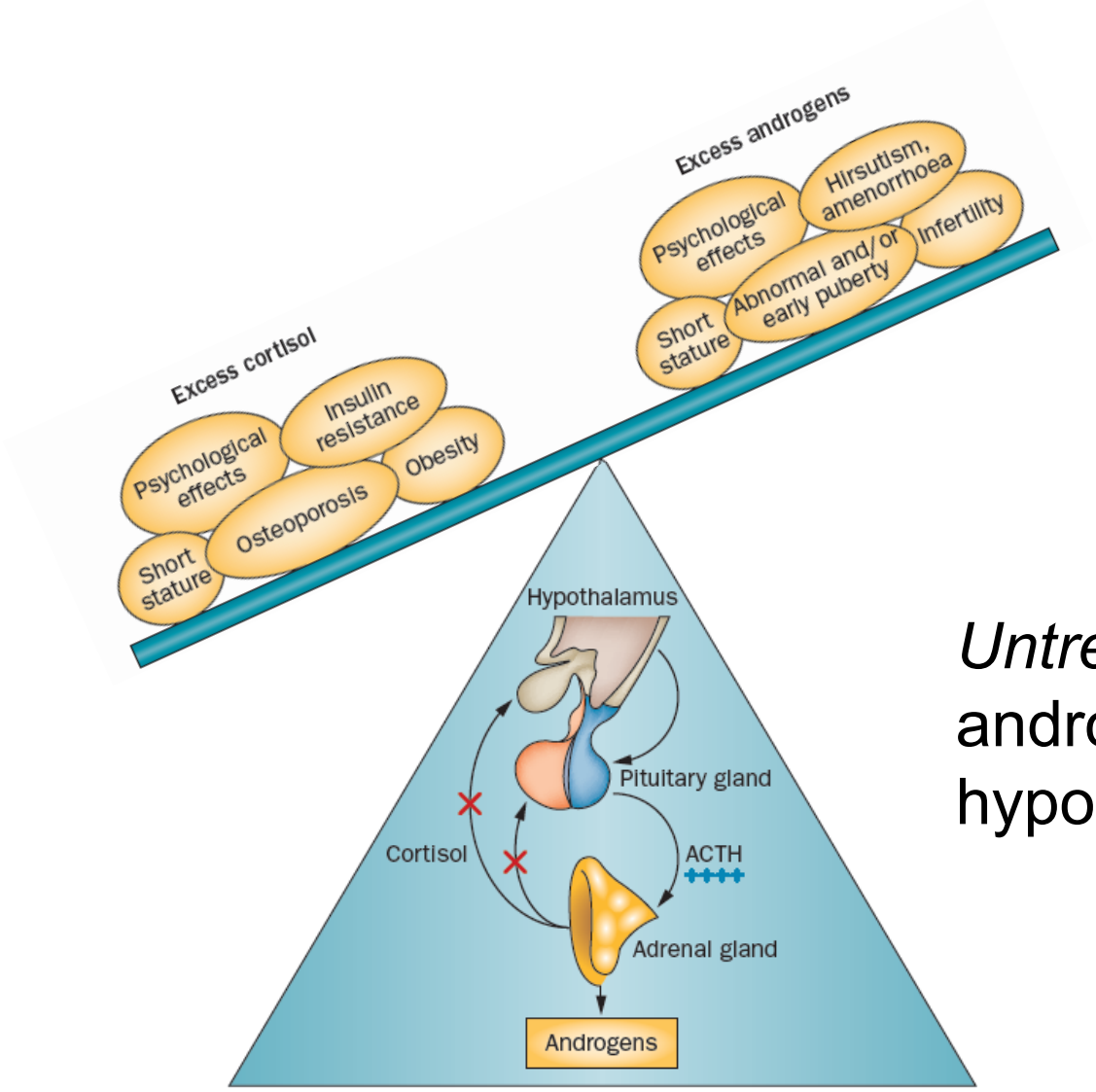
1. Prevent adrenal crisis
2. Reducing signs of androgen excess (hirsutism, acne, oligomenorroe)
3. Fertility
4. Prevention of iatrogenic Cushing's syndrome

Challenge in treatment of (NC)CAH



Han et al, Nature Rev 2014

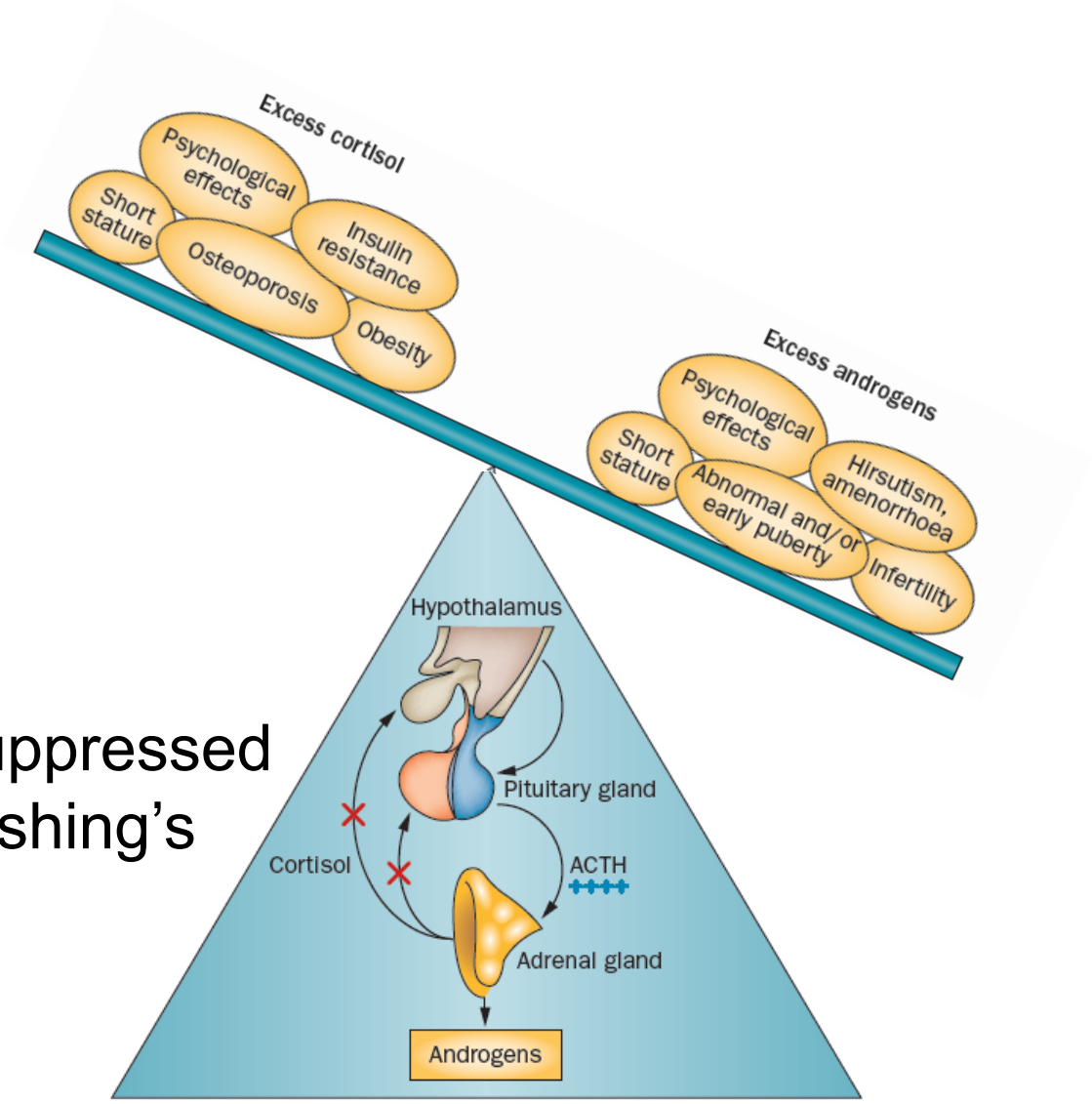
Challenges in treatment of CAH



Untreated:
androgen excess
hypocortisolism

Han et al, Nature Rev 2014

Challenges in treatment of CAH



Treated:
androgens suppressed
iatrogenic Cushing's

Han et al, Nature Rev 2014

Reducing signs of androgen excess in NCCAH

- Glucocorticoid treatment (hydrocortisone, prednisone): variable succes after >6 months
- *Adverse effects*: iatrogenic Cushing's syndrome, iatrogenic adrenal insufficiency
- Consider alternative therapies: oral anti-conceptives, anti-androgens (spironolactone, cyproterone acetate), weight reduction, cosmetic therapy
- Psychosocial support

Fertility in CAH

Fertility may be impaired by several mechanisms

Females

1. Hypogonadotropic hypogonadism (adrenal androgen excess)
2. Elevated progesterone
3. Virilisation, effects of surgery
4. Altered psychosexual development

Reichman et al, Fertil Steril 2014, Bachelot et al EJE 2014

Optimizing fertility in (NC)CAH

Females

- *Strong indication* for (temporaly) glucocorticoid treatment
- Lab goal: normalizing androstenedione, optimal level of 17-OHP unknown
- Lab goal: progesterone <2 nmol/L (follicular phase)
- Ovulation induction: consider clomiphene citrate, gonadotrophins
- Persistent androgen excess: consider bilateral adrenalectomy
- Genetic counseling, mutation analysis partner

Genetic counseling in (NC)CAH

General population Incidence	**Affected** (homozygote)	**Carrier** (heterozygote)
Classic CAH	1: 16000	1: 50
Non-classic CAH	1 : 600	1: 16

≈50% of Non-classic CAH: compound heterozygote (“Severe/Mild”)

Clinical phenotype is dictated by “mildest” mutation

-> Non-classic patient may transfer a “severe” mutation to offspring

probability of NCCAH patient -> CAH child: 1: 400 (1/50 x 1/2 x 1/4)

probability of NCCAH patient -> NCCAH child: 1: 32 (1/16 x 1/1 x 1/2)

Moran et al JCEM 2006:

101 NCCAH mothers, 162 children: CAH 2.5%, NCCAH 14.8%

Reichman et al Fertil Steril 2014, New et al GeneReviews

Genetic counseling in (NC)CAH

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➔ ***Mutation analysis of partner (carrier?)***

Reichman et al Fertil Steril 2014, New et al GeneReviews