Congenital Adrenal Hyperplasia Across the Lifespan

A CSEM Knowledge Transfer Activity

Monday, December 9, 2024

7:00 pm ET

Faculty

Dr. Mimi Kim
CHLA, Los Angeles, CA
Speaker

Dr. Richard Auchus
University of Michigan & Ann Arbor VA Medical Center, Ann Arbor, MI
Speaker

Dr. Sola Mansour
University of Alberta, Edmonton
Moderator

Dr. Liz Rosolowsky
University of Alberta, Edmonton
CSEM CPD Chair

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Accreditation

This activity is an accredited group learning activity under Section 3 as defined by the Royal College of Physicians & Surgeons of Canada for the Maintenance of Certification program.

Approved by CSEM for a maximum of **2.0 hours (credits are automatically calculated)**

CREDITS

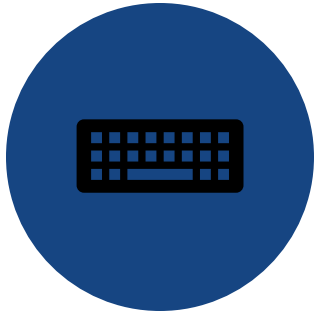
- Complete the evaluation
- 2 weeks post-session, we'll email your results and personal reflection tool
- Review your results
- Reflect using the tool
- Enter your learning outcomes into My MOC

Interaction

- Pre & post tests via Slido – be sure to sign in for your Section 3 credits
- Use the Q&A in Slido to ask questions
- Questions will be answered during discussion time

Participant code: #3986602

Section 3 Self-Assessment Credits



SIGN IN TO SLIDO

PRE-TEST

POST-TEST

REVIEW AND REFLECT

CONFLICT OF INTEREST DECLARATION – Dr. Sola Mansour

I **DO NOT** have a relationship with for-profit/not-for-profit organizations to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organization(s)	Description of relationship(s)
Any direct financial payments including receipt of honoraria		
Membership on advisory boards or speakers' bureaus		
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Patents on a drug, product or device		
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity		

Agenda

7:00 pm Welcome and Introductions – Dr. Sola Mansour

7:05 pm Congenital Adrenal Hyperplasia: Part 1, Childhood – Dr. Mimi Kim

7:50 pm Congenital Adrenal Hyperplasia: Part 2, Adulthood – Dr. Richard Auchus

8:35 pm Q&A

8:45 pm Take-away messages and Wrap Up – Dr. Sola Mansour

Learning Objectives

At the end of this session, participants will be able to:

- Contrast the key management priorities between pediatric and adult patients with CAH, emphasizing clinical differences.
- Outline a structured approach for transitioning adolescents with CAH to adult care, addressing common challenges in care continuity and patient needs.
- Identify and manage long-term disease morbidities, such as cardiovascular and metabolic risks, in CAH patients.

Pre-test Questions

- Ensure you are signed in to Slido: Name, Email
- Slido.com with code:

Participant code: #3986602

CONGENITAL ADRENAL HYPERPLASIA ACROSS THE LIFESPAN

PART 1: CHILDHOOD & ADOLESCENCE

Mimi Kim, MD MSc
Associate Professor of Clinical Pediatrics
Co-Director, CHLA CAH Comprehensive Care Center

mskim@chla.usc.edu

CSEM SCEM
The Canadian Society of Endocrinology and Metabolism
La Société canadienne d'endocrinologie et de métabolisme

Children's Hospital LOS ANGELES

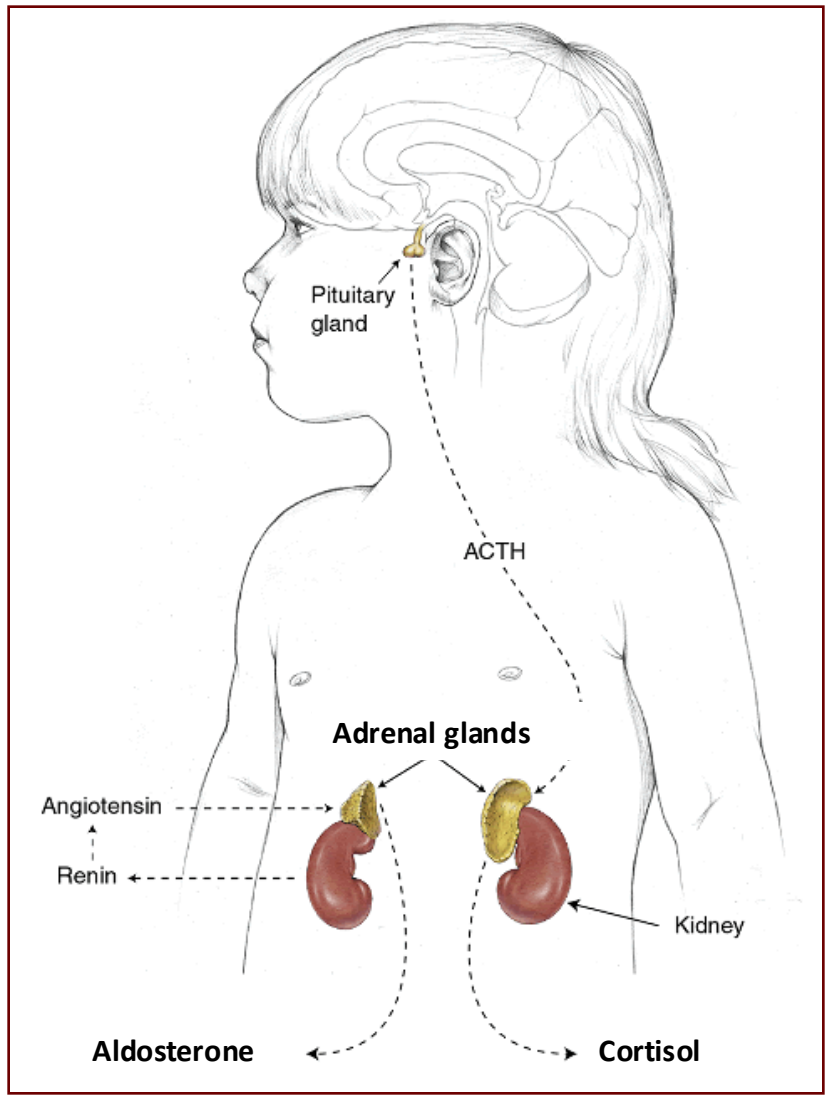
USC

CONFLICT OF INTEREST DECLARATION – Dr. Mimi Kim

I **DO** have a relationship with for-profit/not-for-profit organizations to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organization(s)	Description of relationship(s)
Any direct financial payments including receipt of honoraria	UpToDate	Author Royalties (Adrenal Insufficiency chapters)
Membership on advisory boards	Neurocrine Bioscience/Diurnal LTD Spruce Biosciences Eton Pharmaceuticals	Advisory Board Steering Committee member Advisory Board
Funded grants or clinical trials	Neurocrine Bioscience/Diurnal LTD Spruce Biosciences	Research Funding – Site PI

CONGENITAL ADRENAL HYPERPLASIA (CAH)



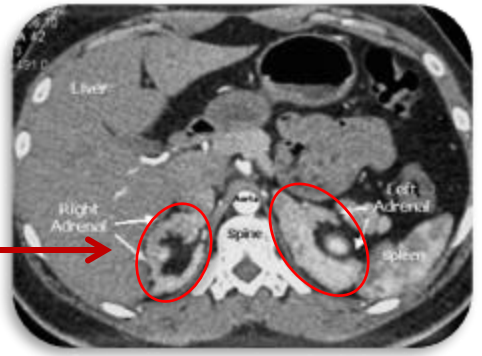
www.hopkinschildrens.org/cah/images

- Most common cause of primary adrenal insufficiency in children & adolescents
- Monogenic disorder of adrenal steroidogenesis

  CYP21A2

  - 1:15000 (classical)
  - 1:1000 (non-classical)
  - 1/60 carrier rate
- 21-hydroxylase deficiency = 95% of cases

Adrenal hyperplasia
if untreated (CT scan)



CAH: Cortisol & Aldosterone Deficiency

ACTH

Cholesterol

Pregnenolone → 17-OH-Pregnenolone

3β HSD

→ 17-OH-Progesterone

21α-Hydroxylase

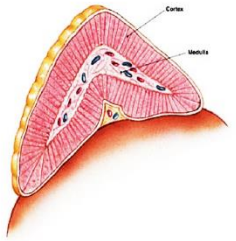
11-hydroxylase

Aldosterone

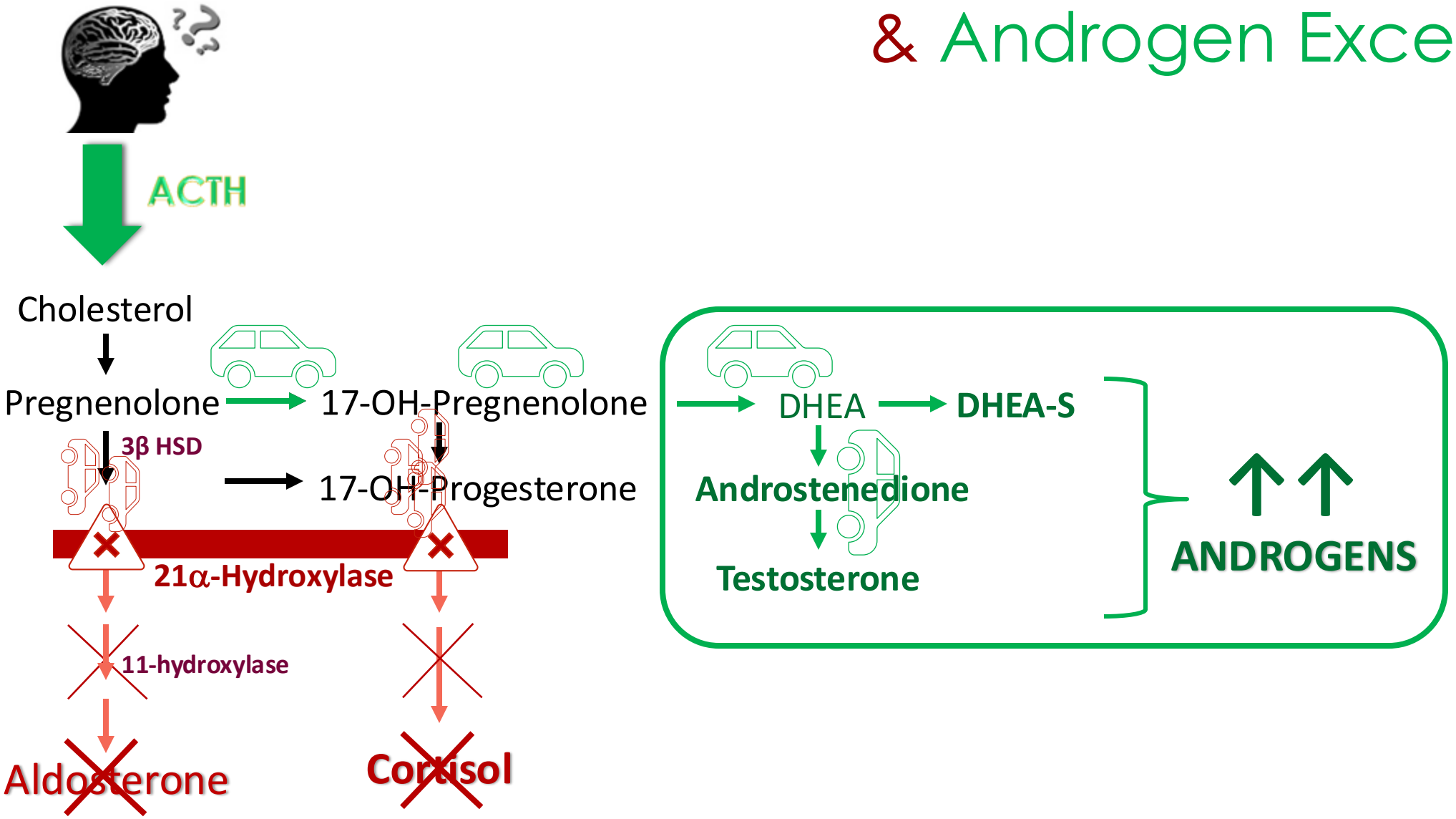
Cortisol

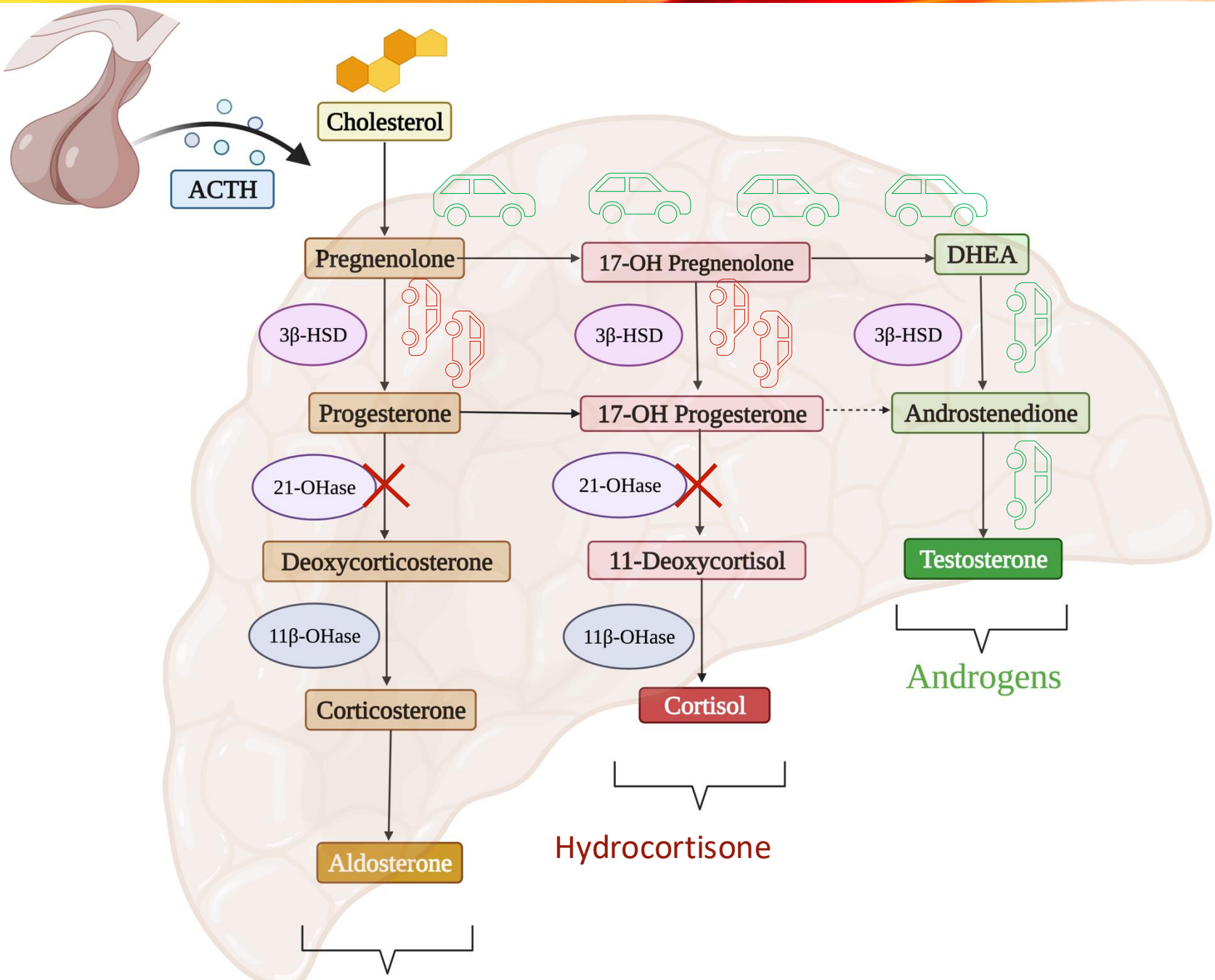
Traffic Jam

STEROIDOGENIC PATHWAY (enzyme defect)



CAH: Cortisol Deficiency & Androgen Excess





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Fraga N… Kim MS, *Pediatr in Rev*, 2024

Pre-Test Question 1

A 7 YO boy with classic 21-hydroxylase deficiency has had erratic hormone control over the last 3 years. He presents with 3 months of increasing pubic hair growth, body odor, and acne. He also exhibits rapid growth and a bone age advancement of 3 years (current BA = 11 y).

Laboratory data:

Androstenedione 120 ng/dL (4.2 nmol/L); Testosterone 150 ng/dL (5.2 nmol/L);

17-hydroxyprogesterone 15,100 ng/dL (457.5 nmol/L).

Normal electrolytes and plasma renin activity level.

slido

Please download and install the Slido app on all computers you use

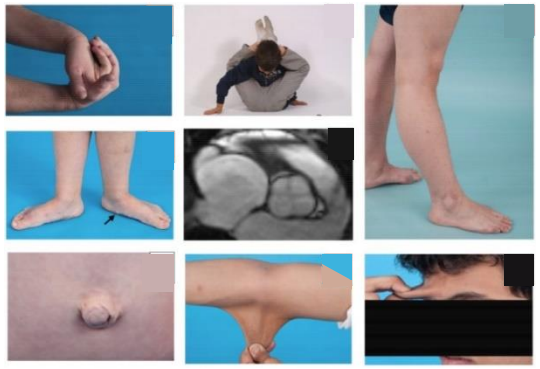
Q1a: What laboratory test will identify the reason for his sudden androgen excess?

ⓘ Start presenting to display the poll results on this slide.

Wide Range of Clinical Severity

Severe (classic) → **Mild (non-classic)**

CAH-X Syndrome

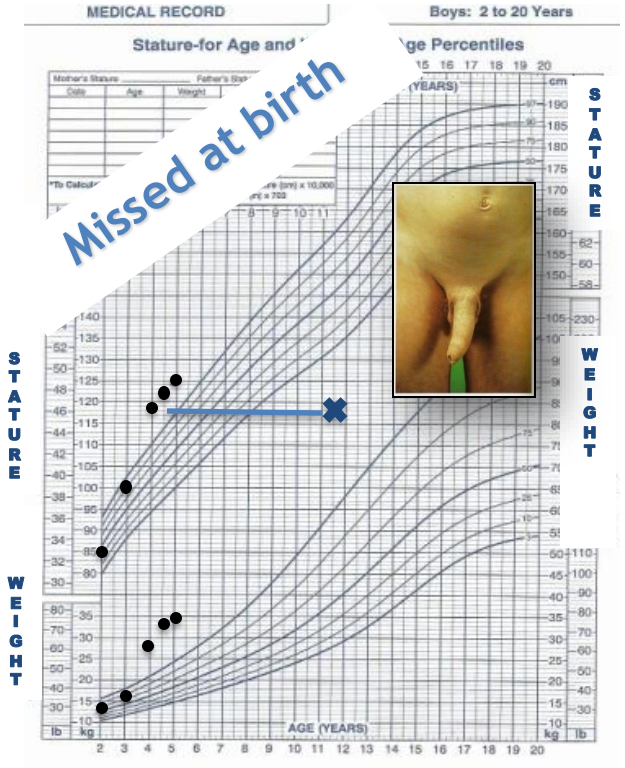


Salt-wasting

Virilized External Genitalia ♀

Acutely ill male

Non salt-wasting (simple-virilizing)



NCAH Spectrum:
Asymptomatic --
Premature pubarche --
Irregular periods --
Infertility

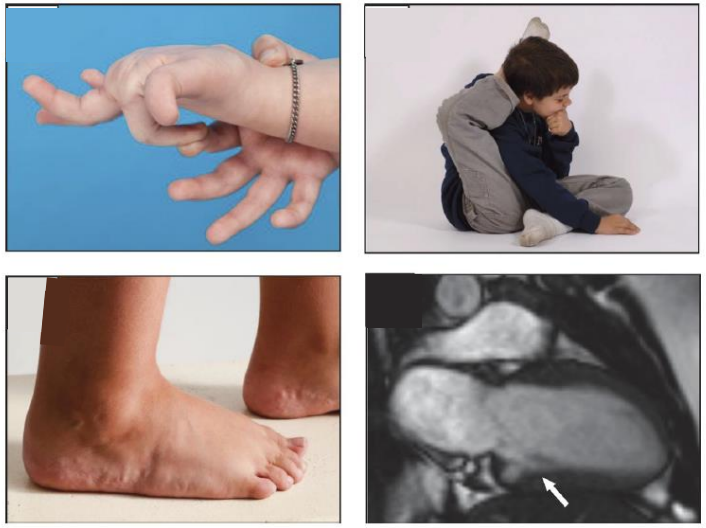
*** Mandatory NBS is changing the care of CAH**

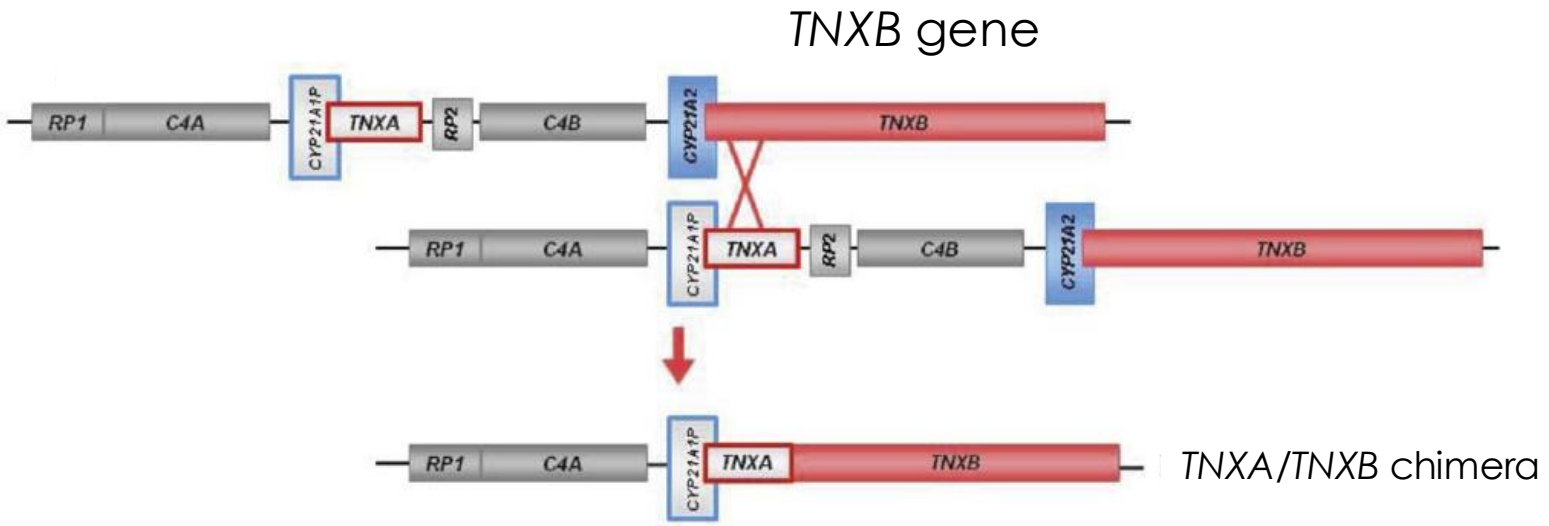
- **Alberta NBS for CAH since 2007**

Miller & Merke, *HRP*, 2018

Bornstein & Merke, *Lancet*, 2005

CAH-X Syndrome





Unequal crossover during meiosis resulting in a ***TNXA/TNXB* chimera**

Contiguous Gene Deletion Syndrome

Overlapping symptoms with Ehlers-Danlos

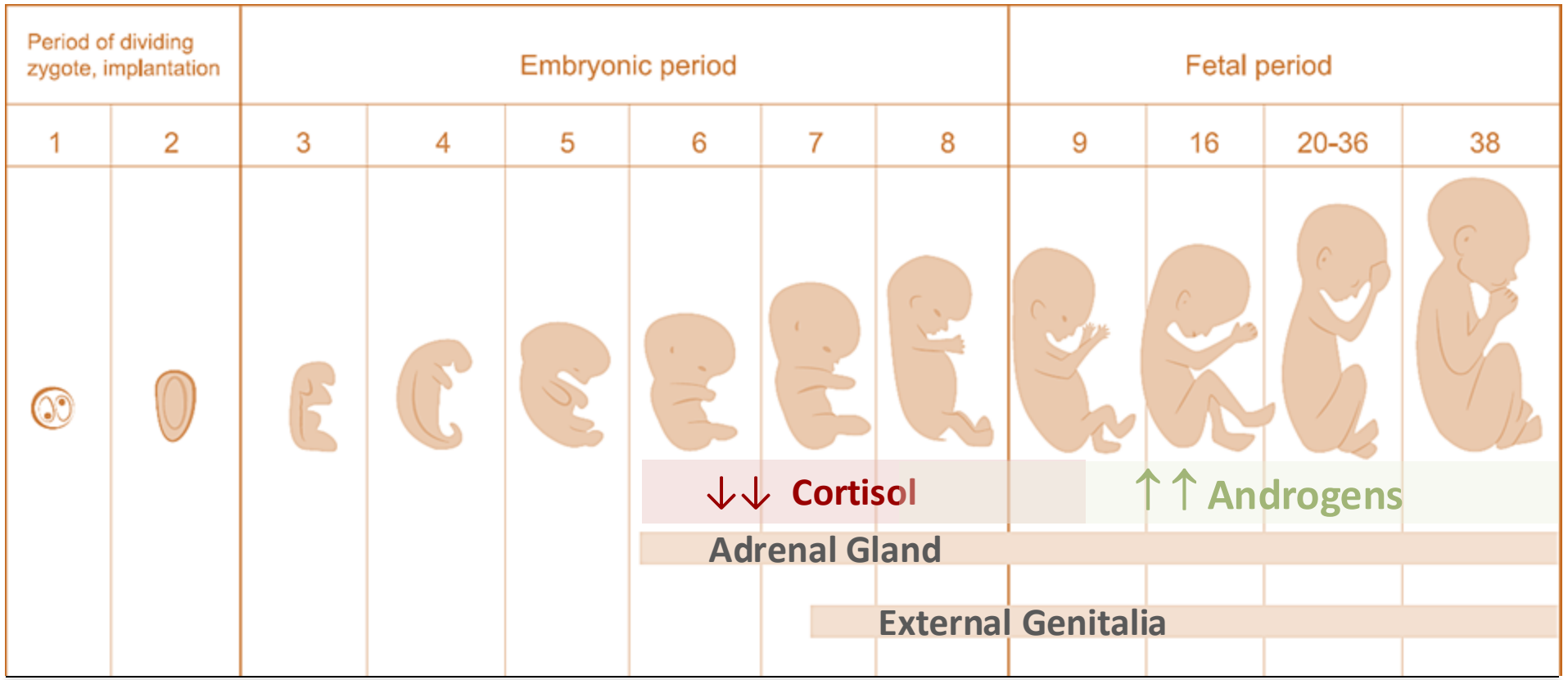
- Hypermobile joints
- Flat feet
- Heart abnormalities (e.g. valvular)

Miller & Merke, *HRP*, 2018

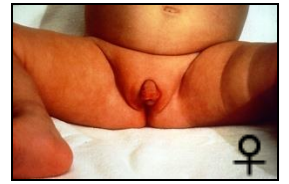
CAH: Altered Intrauterine Environment

Pathological Adrenal Gland *in utero*

Severe (classical)



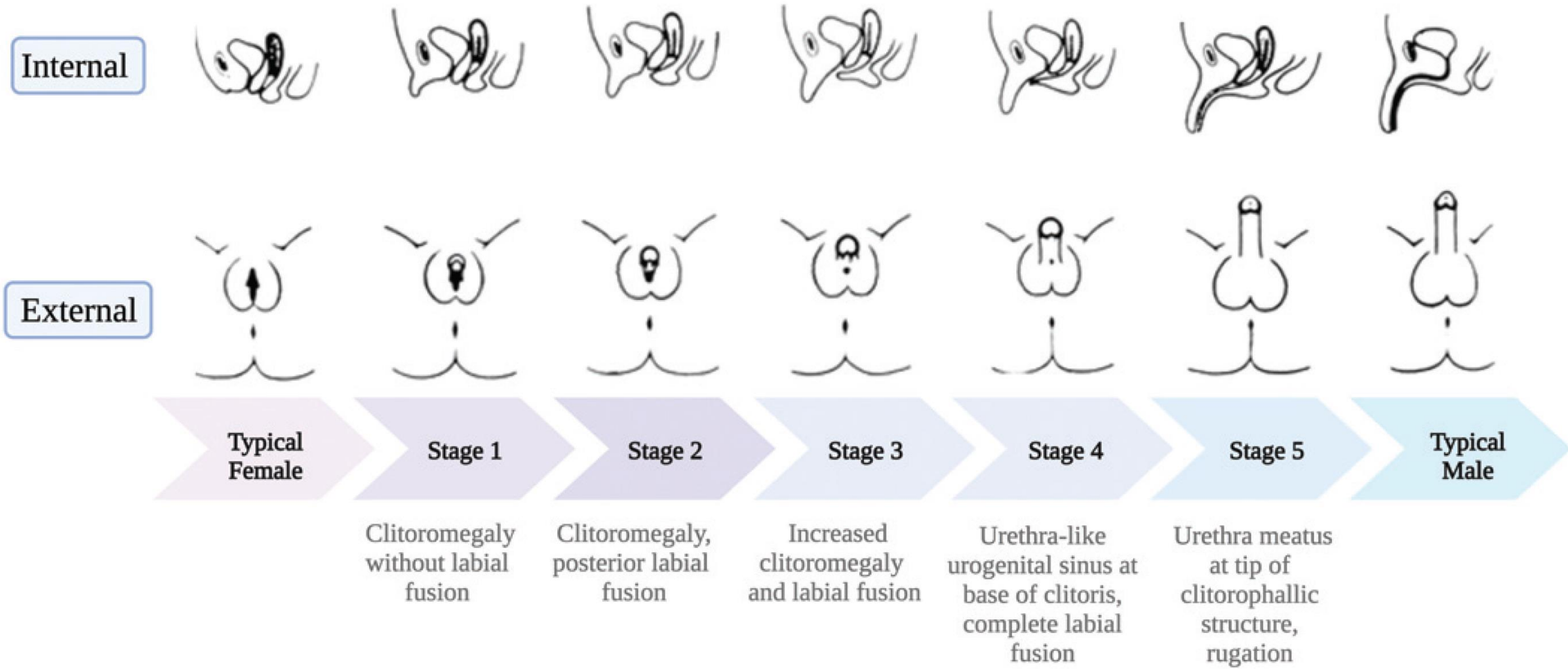
Androgen Excess
(CAH: early programming)



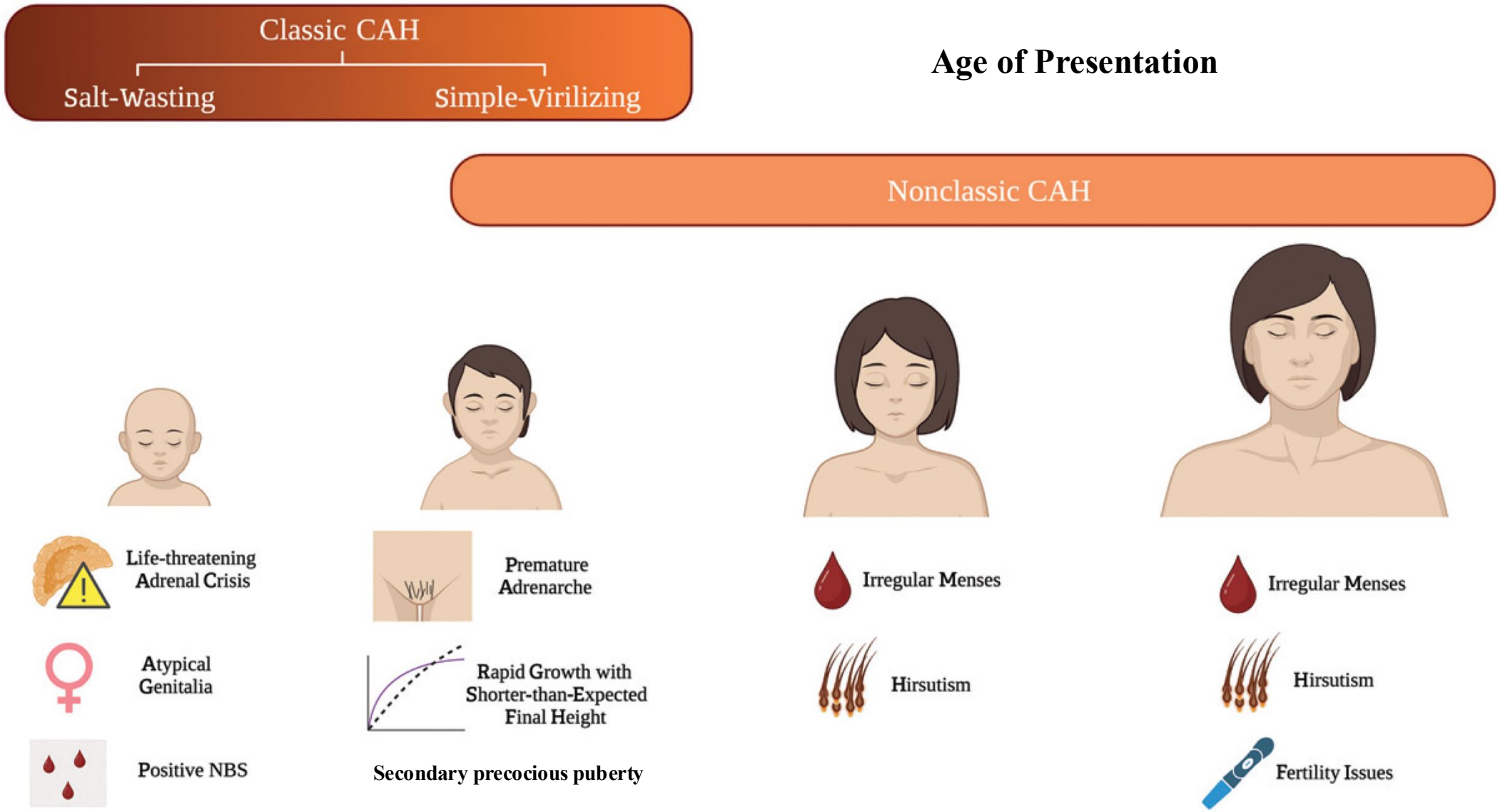
Virilized
Atypical Genitalia

First Trimester

Prenatal Androgen Exposure



Fraga N… Kim MS, *PIR*, 2024



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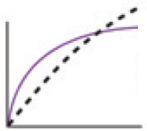
Management Considerations




Adrenal Insufficiency

Age matters!

CVD Risk
Bone Health
Transition
Mood



Normal Growth & Puberty

Virilization

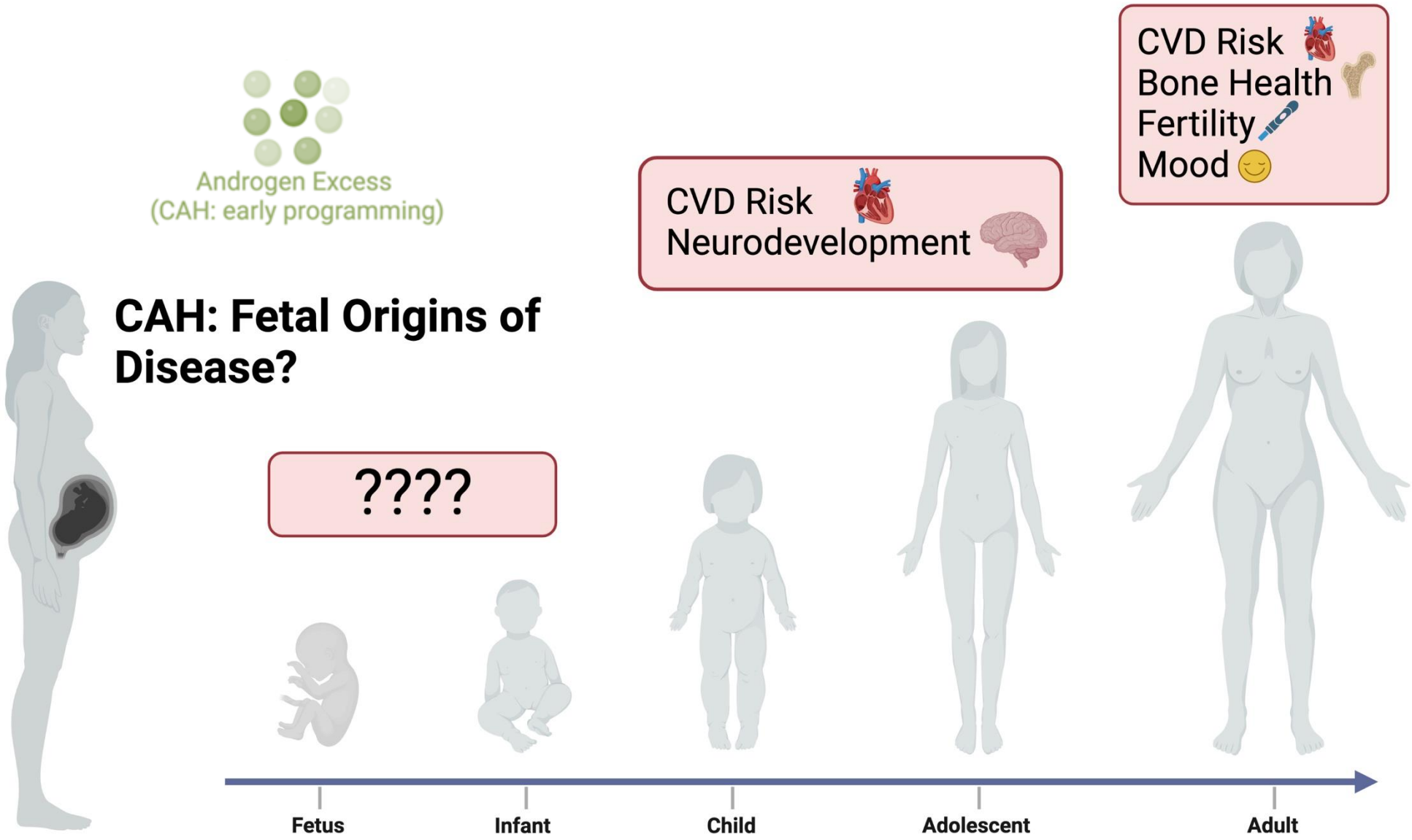
Irregular Menses

Fertility Issues

Hirsutism

Ovarian Health
TART

CAH: Co-morbidities and lifetime risk



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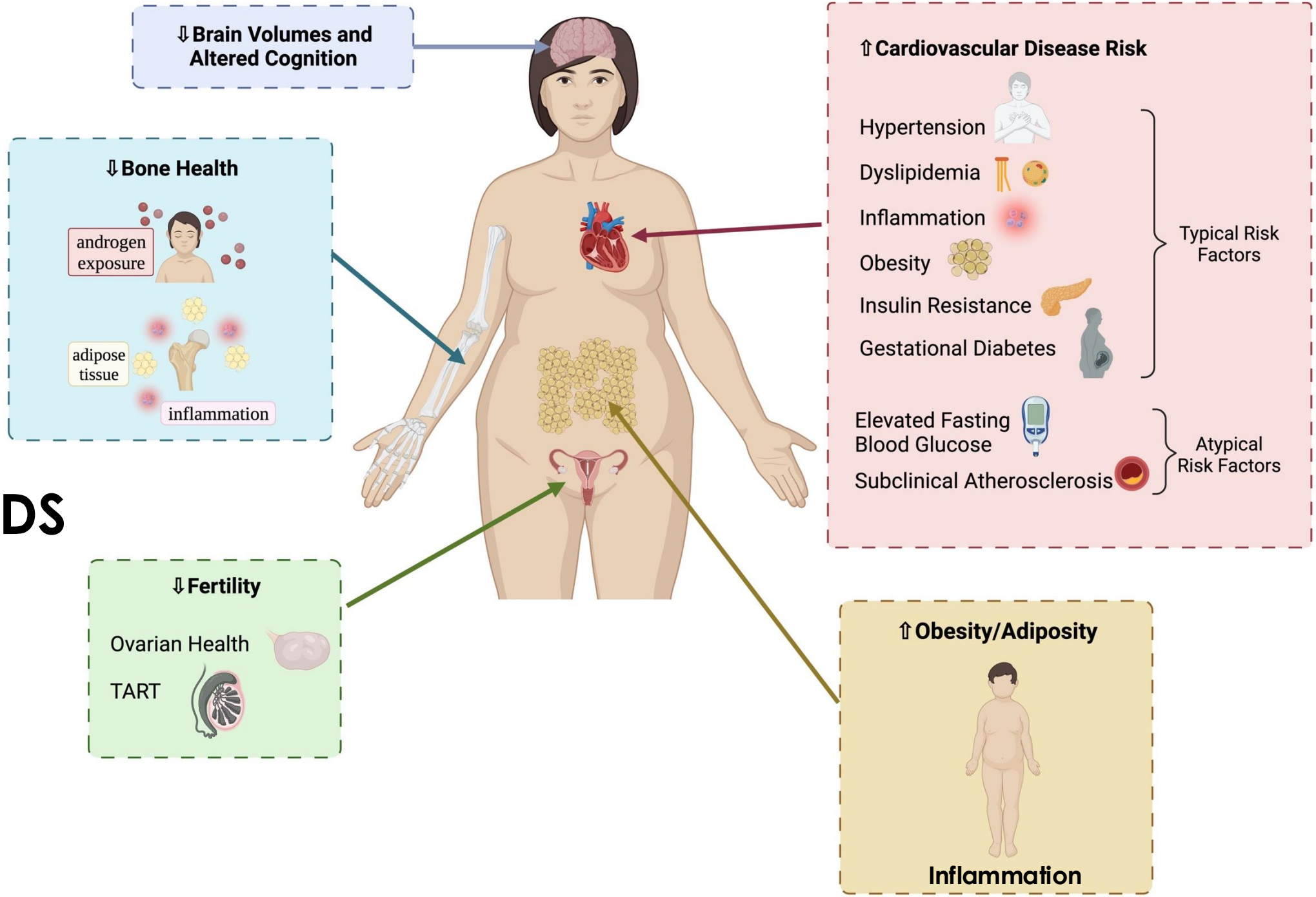
UNMET NEEDS IN CAH



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Congenital Adrenal Hyperplasia (CAH) Comprehensive Care Clinic

Children's Hospital LOS ANGELES

Dr. Mitchell Geffner — Clinic Co-Directors

Dr. Mimi Kim — Clinic Co-Directors

A CARES Foundation
Medical and Surgical Center of Excellence

Since 2015

Dr. Roger De Filippo — Surgical Center Director

Dr. Anna Ryabets — Bone Metabolism

Janet Guerrero — Clinic Coordinator

Dr. Linda Randolph — Geneticist

Dr. Cynthia Munoz — Clinic Psychologist

Gail Hubbard — Genetic Counselor

Brenda Manzanarez, RD — Clinical Dietitian

Julie Yllescas — Clinic Social Worker

Alice Koopmans — Nurse Educator

Irene Klecha — Nurse Perinatal Care Manager

OUR SERVICES:

- Endocrinology consultation
- Pediatric Urology consultation (and state-of-the-art surgical repair as needed)
- Perinatology consultation (The Institute for Maternal Fetal Health)
- Genetics consultation and counseling
- Behavioral Health consultation
- Nutritional consultation
- State-of-the-art radiological imaging
- Education and training for families and medical professionals
- Stress-dose teaching
- Gynecology
- Dermatology
- Reproductive Endocrinology and Adult Urology (Keck School of Medicine of USC)
- Annual Adrenal Camp at The Painted Turtle
- Ongoing family support and education events
- Transition to adult care (in progress)

chla.org/CAH

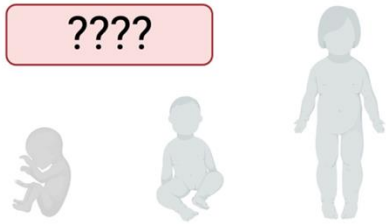
CAH CENTER OF EXCELLENCE

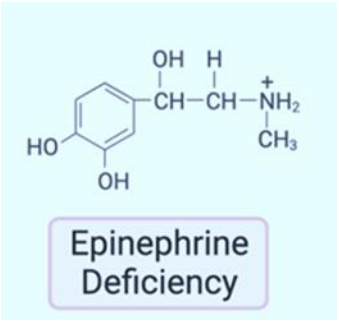
Natural History from Infancy
N = 200

Infant Studies
- **Illness, Epinephrine**
- **TART**
- **Brain Development**

Pediatric/Young Adult
- **CVD Risk Factors**
- **Fertility**
- **Bone Health**
- **Neuropsychology**

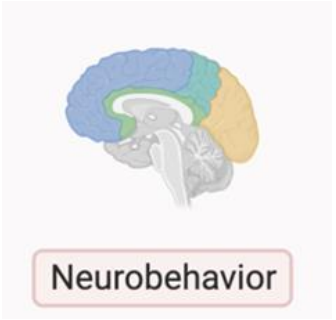
INFANT-TODDLER CAH STUDIES

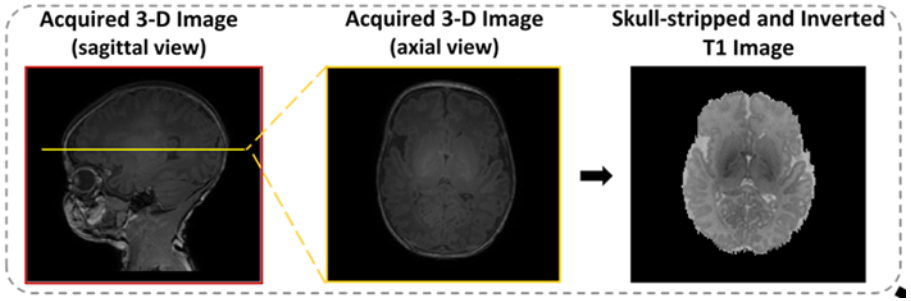




Infants with CAH have lower epinephrine levels than controls, indicating that impaired adrenomedullary function may occur during fetal development and be present from birth.

Testicular Adrenal Rest Tumors were not found in 31 scans in males with classical CAH 0-4 y despite settings with expected high ACTH drive.





Do newborns with CAH have affected brain volumes?

Rajagopalan et al. HRP 2023; Kim et al. HRP 2019; Kim et al. JCEM 2014

CAH: INFANT-TODDLER BRAIN

Vidya Rajagopalan, PhD

Hormone Research in Paediatrics

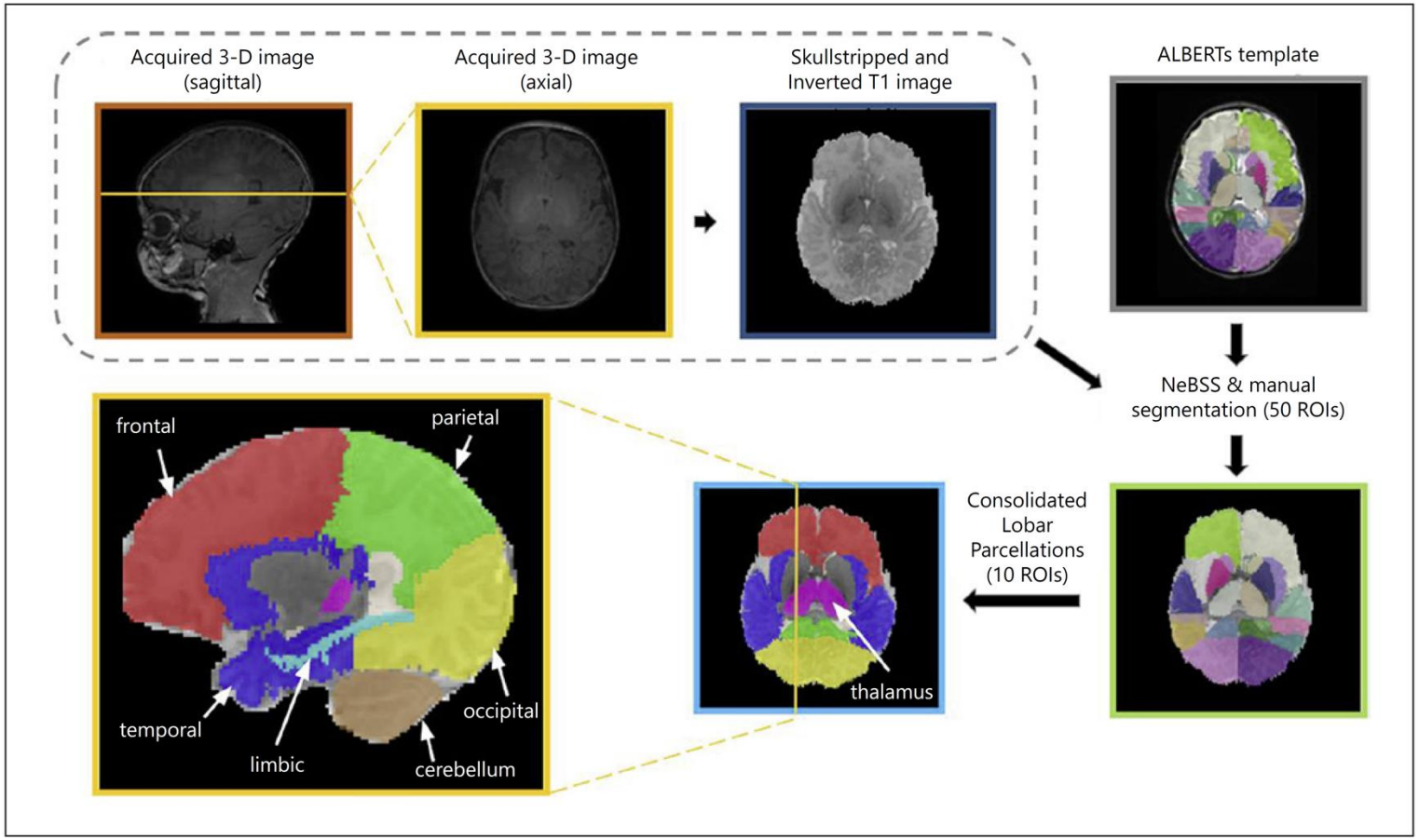
Research Article

Horm Res Paediatr
DOI: 10.1159/000529403

Received: November 28, 2022
Accepted: January 19, 2023
Published online: February 1, 2023

Infants with Congenital Adrenal Hyperplasia Exhibit Thalamic Discrepancies in Early Brain Structure

Vidya Rajagopalan[a, b] Lloyd N. Overholtzer[c] William S. Kim[c]
Jessica L. Wisnowski[a, d] Trevor A. Pickering[e] Nicole R. Fraga[c] Joyce Javier[f]
Liza Mackintosh[f] Christine Mirzaian[f] Mitchell E. Geffner[b, c] Mimi S. Kim[b, c]

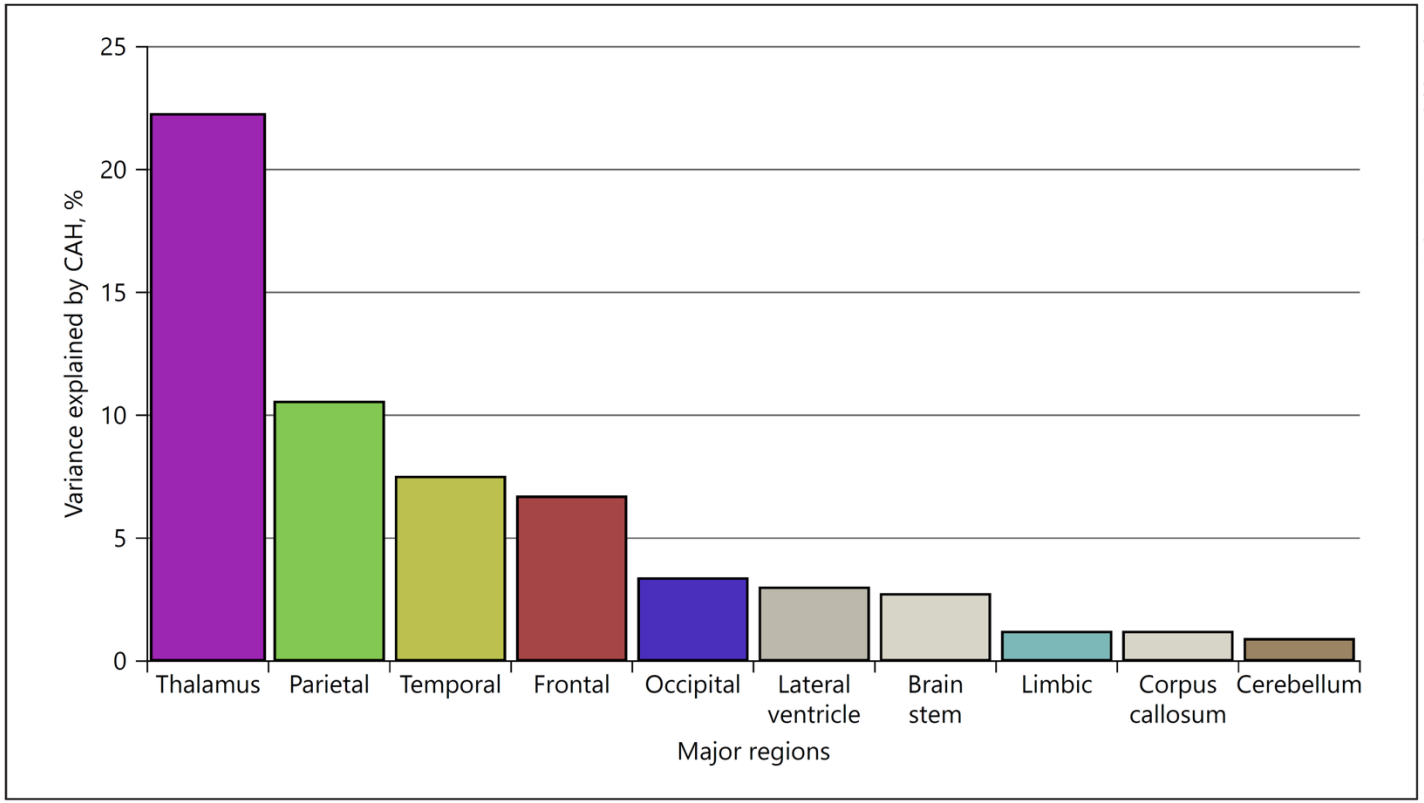


Rajagopalan V … Kim MS. HRP 2023

CAH: INFANT-TODDLER BRAIN

Infants with CAH (n = 16) have smaller thalamic volumes compared to controls, suggesting a prenatal influence on brain development in CAH.

- Thalamic emergence at 8–14 weeks makes the region particularly vulnerable to changes in the intrauterine environment, with potential implications for later maturing brain regions.

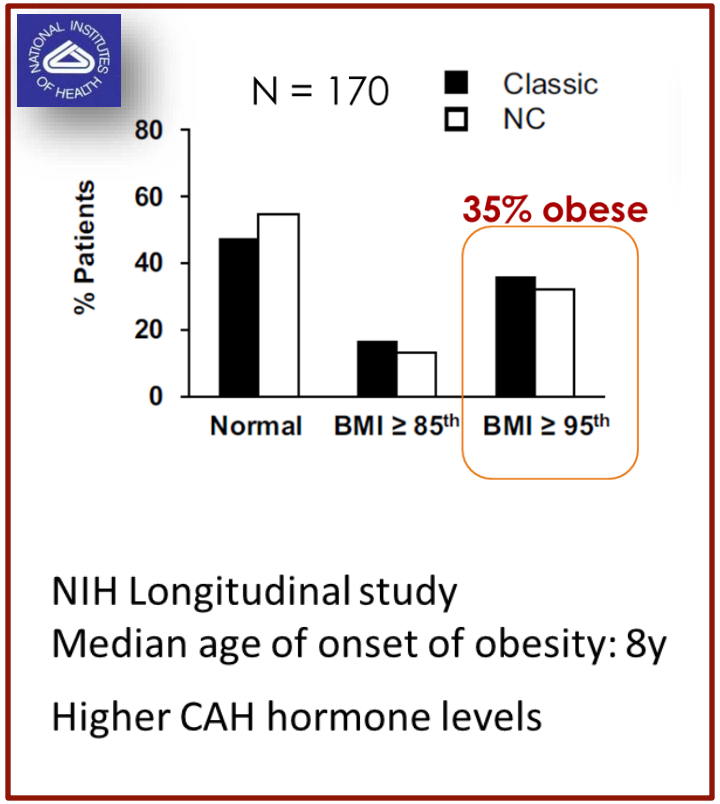


Degree to which each brain region was differentiated between CAH and control infants. *Relaimpo* analysis.

Rajagopalan V … Kim MS. HRP 2023

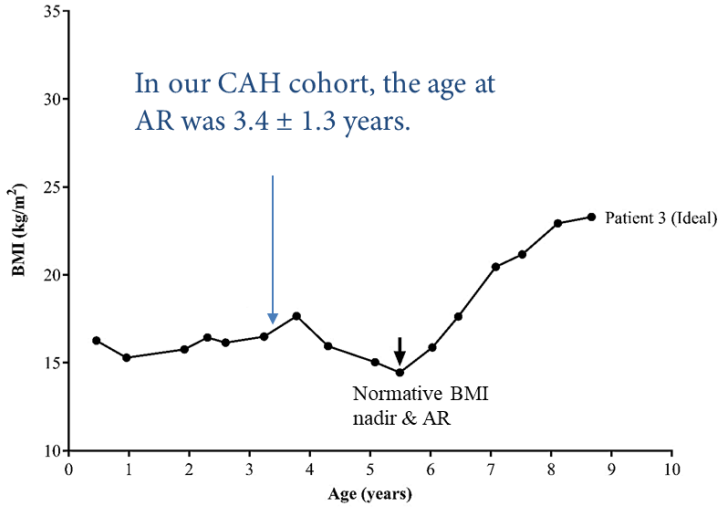
CAH YOUTH AND OBESITY

- Obesity in youth with CAH **exceeds** epidemic rates in the general population, starts **early**, and could represent a **more severe** obesity phenotype.



NIH Longitudinal study
Median age of onset of obesity: 8y

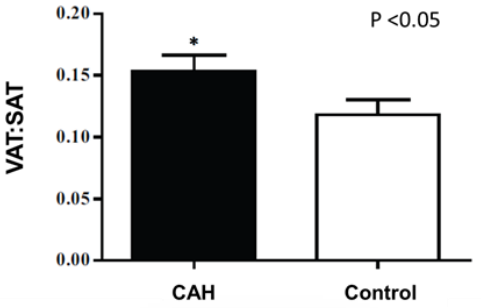
Higher CAH hormone levels

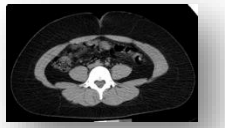


Early Adiposity Rebound

Increased VAT:SAT constitutes an adverse metabolic phenotype in obese adolescents.

(Caprio, Am J Physiol 1996)



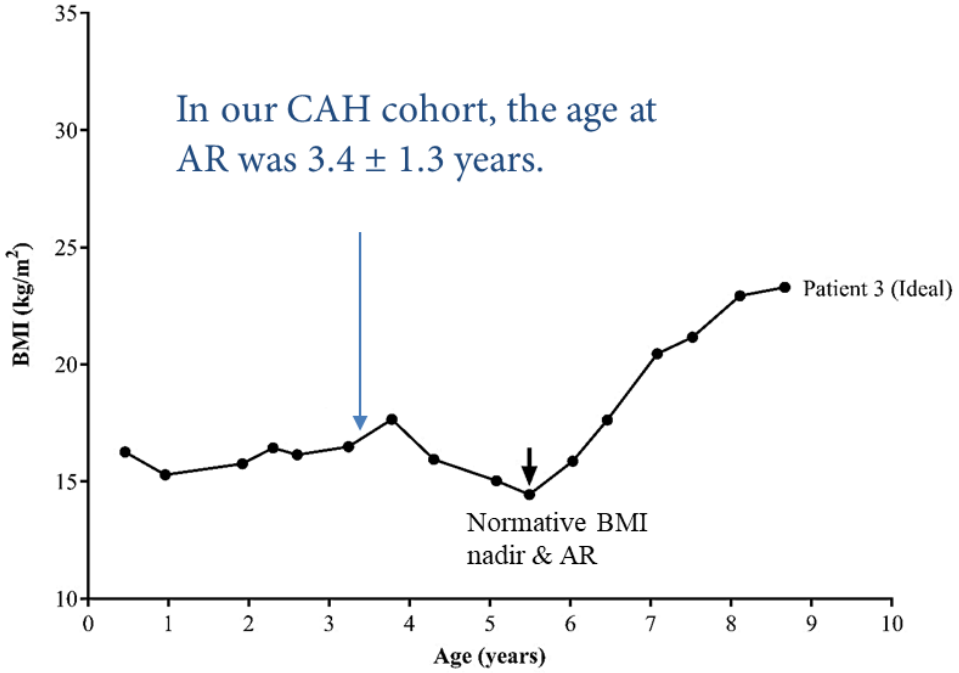


Finkielstain & Kim et al, JCEM 2012
Torky A, et al. JCEM 2021

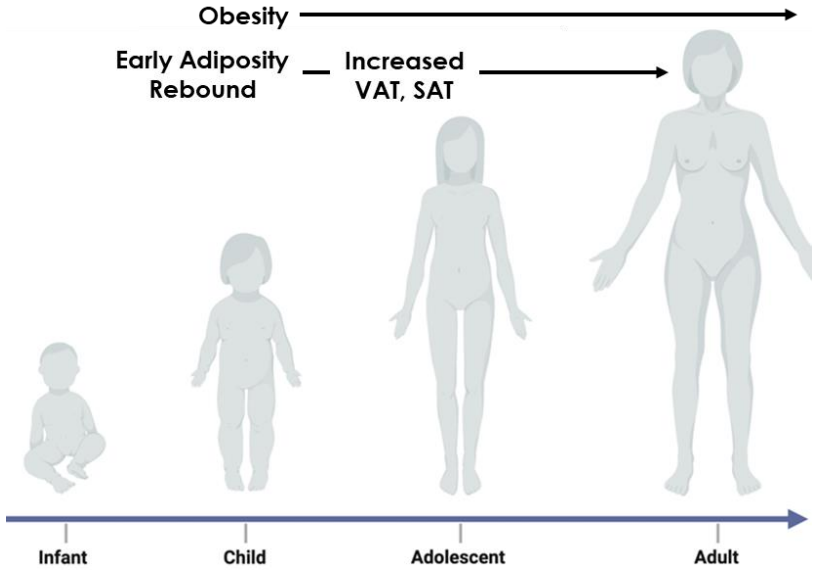
CAH: OBESITY FROM EARLY LIFE

Early Adiposity Rebound Predicts Obesity and Adiposity in Youth with Congenital Adrenal Hyperplasia

Gagandeep Bhullar[a] Veeraya K. Tanawattanacharoen[a] Mei Y. Yeh[a]
William S. Kim[a] Alaina P. Vidmar[a, b, c] Mitchell E. Geffner[a, b, c]
Darryl H. Hwang[b] Mimi S. Kim[a, b, c]



An earlier AR predicted ↑ BMI-z in childhood, ↑ waist circumference and total body fat



- Patients with CAH exhibit an earlier adiposity rebound (AR) compared to normative populations in UK (1.5y), USA and Japan (3y).

Bhullar G … Kim MS, HRP, 2020

CAH & OBESITY: ETIOLOGIES?

Hormone imbalances inherent to CAH?

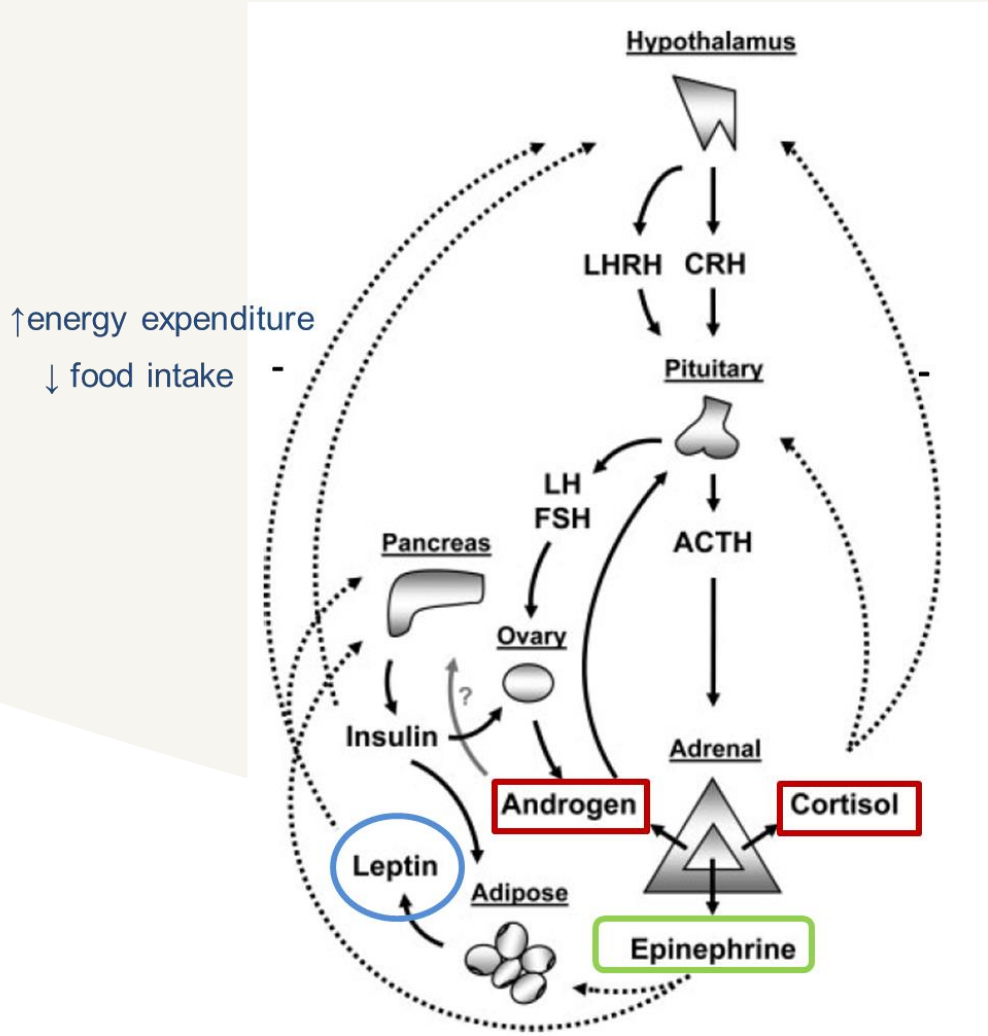
There could be a pathological role for androgen excess or a lack of protective effect from estrogen

Familial factors such as maternal obesity can contribute to the increased incidence of obesity seen in CAH.

(NIH: Torky A et al. JCEM 2021)

Associations between GC dosing and obesity are seen primarily in adults, not children.

OTHER?



Kim and Merke, *Semin Repro Med* 2010

Post-Test Question 1

A 7 YO boy with classic 21-hydroxylase deficiency has had erratic hormone control over the last 3 years. He presents with 3 months of increasing pubic hair growth, body odor, and acne. He also exhibits rapid growth and a bone age advancement of 3 years (current BA = 11 y).

Laboratory data:

Androstenedione 120 ng/dL (4.2 nmol/L); Testosterone 150 ng/dL (5.2 nmol/L);

17-hydroxyprogesterone 15,100 ng/dL (457.5 nmol/L).

Normal electrolytes and plasma renin activity level.

slido

Please download and install the Slido app on all computers you use

Q1b: What laboratory test will identify the reason for his sudden androgen excess?

ⓘ Start presenting to display the poll results on this slide.

CAH MEDICATIONS

Pre-Test Question 2

A 14 YO girl with classic 21-hydroxylase deficiency returns for evaluation. Menarche occurred at age 12 but periods have been irregular (every 4-10 weeks), and she grooms her facial hair twice weekly.

She has been treated with TID hydrocortisone (15 mg / 5 mg / 5 mg = 16.4 mg/m^2/d) and fludrocortisone 0.1 mg AM for the last year, and she has gained 8 kg over this time. Her BMI is 32 kg/m^2, and she does not want to take more hydrocortisone due to weight gain. She is also bothered by the facial hair and need to groom. Her bone age is 15 4/12 years.

Physical exam shows central obesity, shaved stubble on her chin, and Tanner 5 breasts and pubic hair.

Laboratory data:

Androstenedione 216 ng/dL (7.5 nmol/L); Testosterone 68 ng/dL (2.4 nmol/L);
Sex-Hormone Binding Globulin (SHBG) 35 nmol/L; Fasting glucose 90 mg/dL (5 mmol/L).

Normal electrolytes and plasma renin.

slido

Please download and install the Slido app on all computers you use

Q2a: What additional medication would most effectively lessen the androgen exposure without more glucocorticoid exposure and help to regularize her menses?

ⓘ Start presenting to display the poll results on this slide.

HORMONE REPLACEMENT

Aldosterone:
Fludrocortisone

- 0.1 mg daily (typical dose)

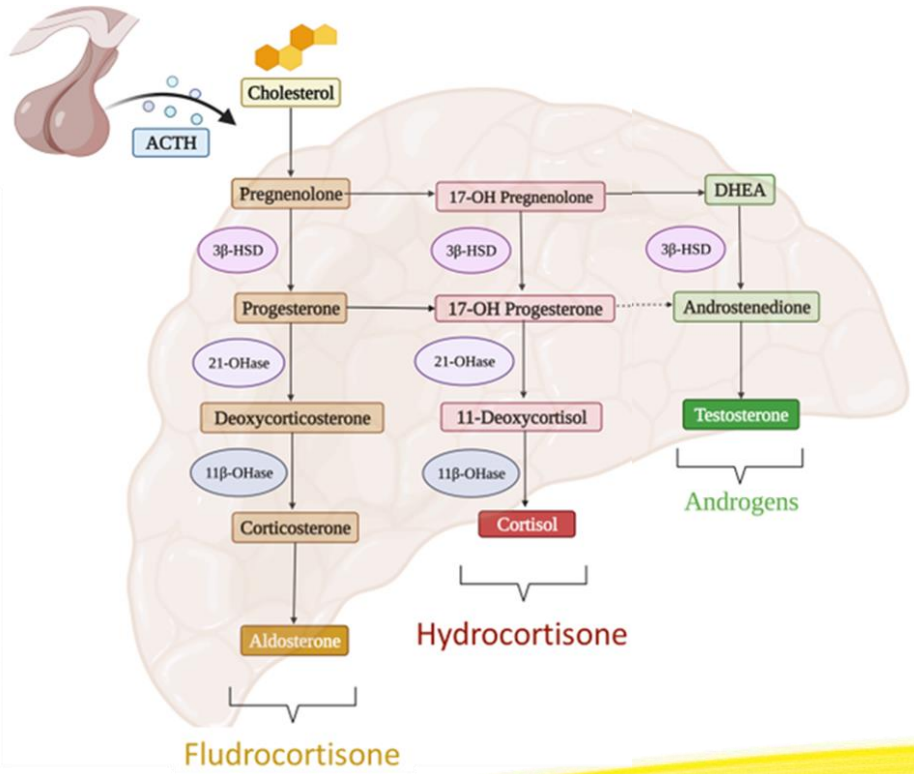
NaCl

- (Injectable) Solution
- Tablets 1000 mg
- Capsules (Walgreens)
- Table salt
- Electrolyte powder

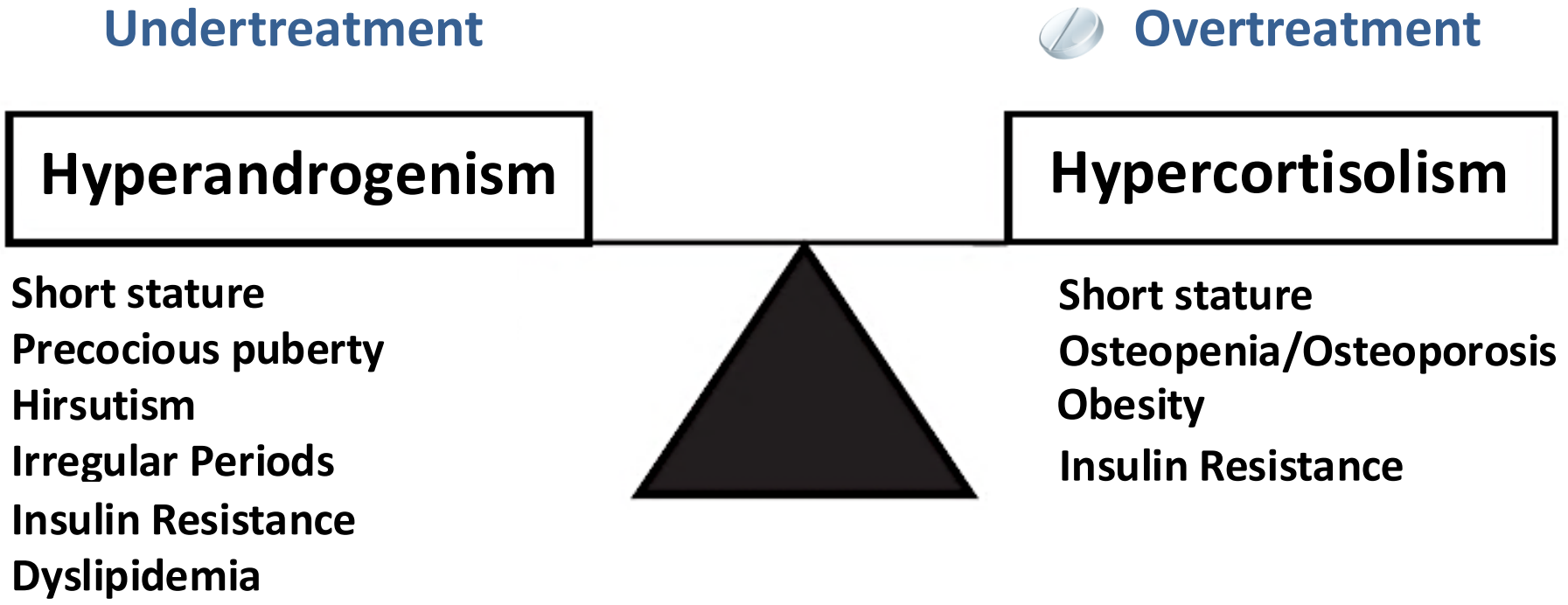
Cortisol:
Hydrocortisone

Growing children

- Tablets
- Capsules
- Solu-Cortef



CAH Management: A Balancing Act

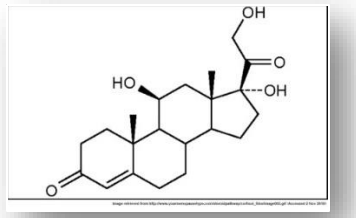


Pediatric Treatment Goal: Achieve normal growth and development (and decrease co-morbidity)

Bornstein & Merke, *Lancet,* 2005

(Short) History of Hydrocortisone

1930's:
Cortisol
structure
is discovered



1940's:

Cortisone

1950:

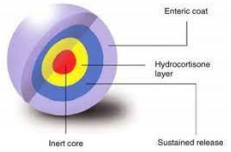
Nobel Prize (physiology / medicine) for the discovery of Cortisol

(Kendall, Reichstein, Hench)

1955:

Hydrocortisone

Innovative Delivery



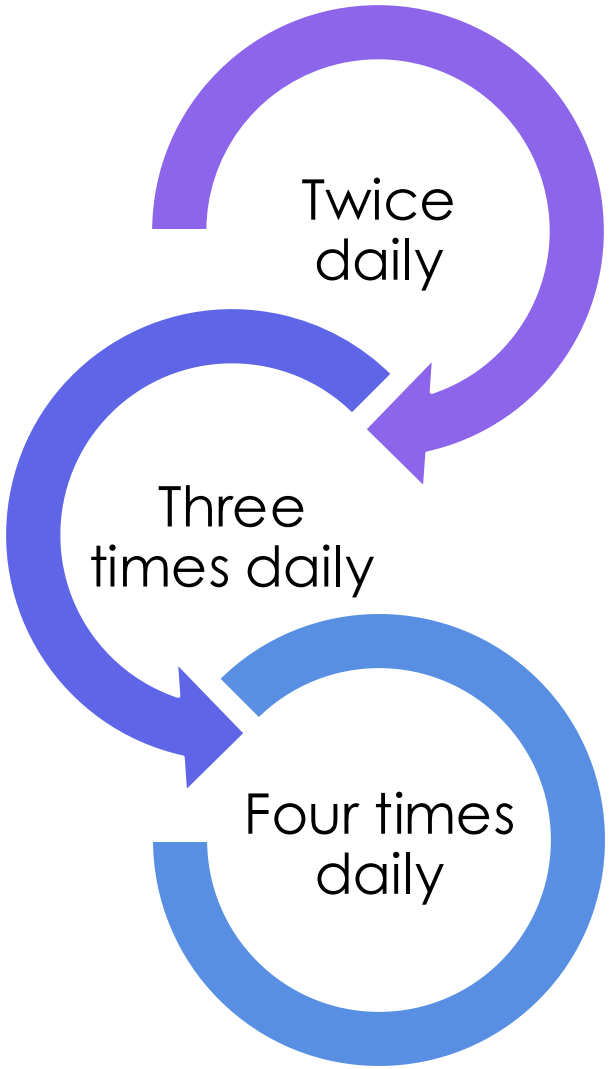
Novel Glucocorticoid

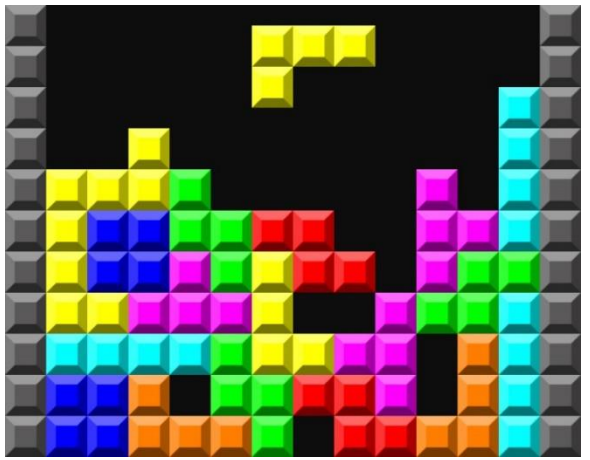
Modified release (Efmody)
Development name: Chronocort

Capsules (Alkindi sprinkles)

Pump

HYDROCORTISONE DOSING



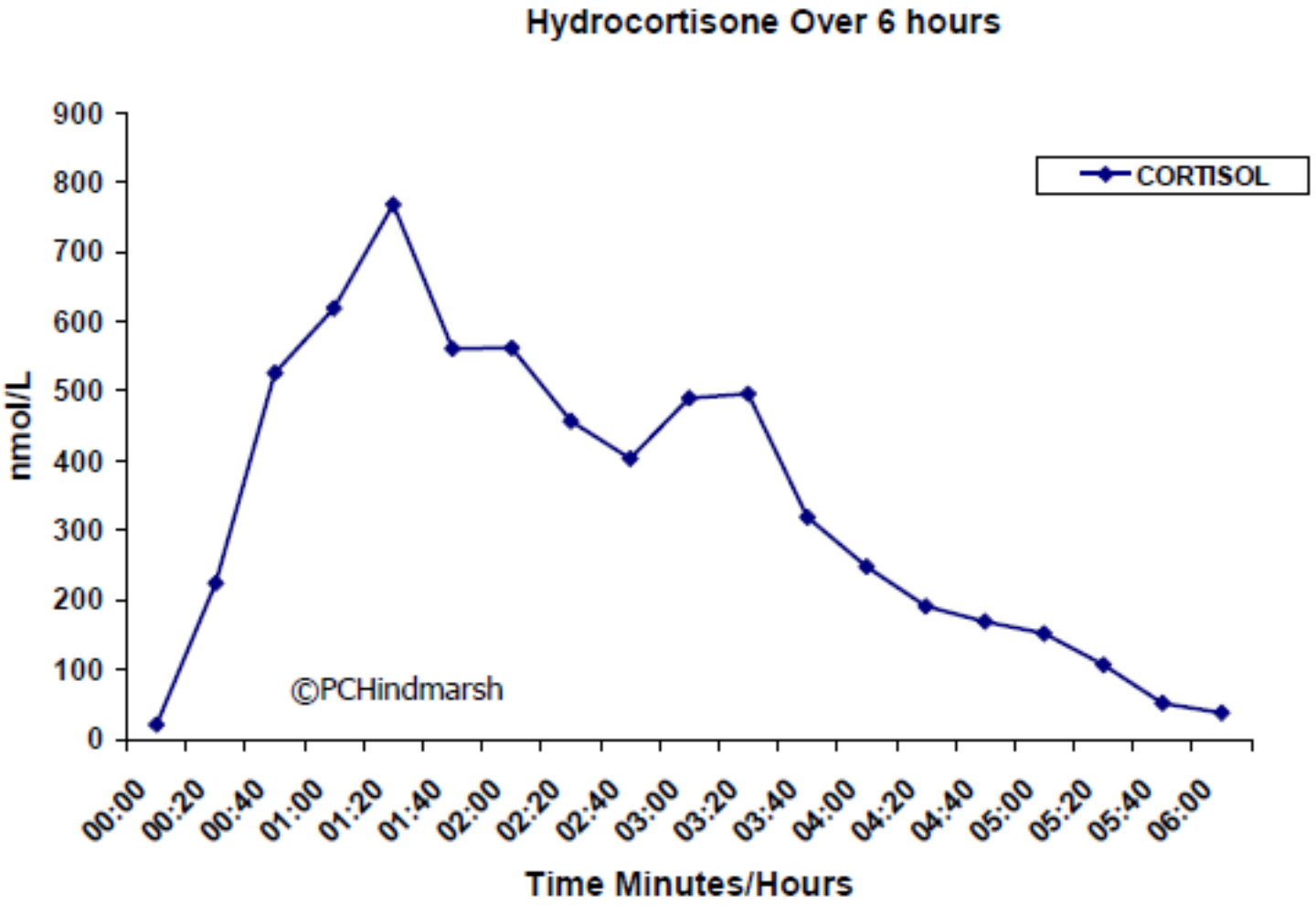


Medication tetris

- Circadian rhythm?
- Duration of action (6 hours)

What Happens When You Take Hydrocortisone?

- Absorbed from gut
- Half-life of 1.7 hours
- Peak cortisol levels an hour
- Rapid decline - Lasts 6 hours

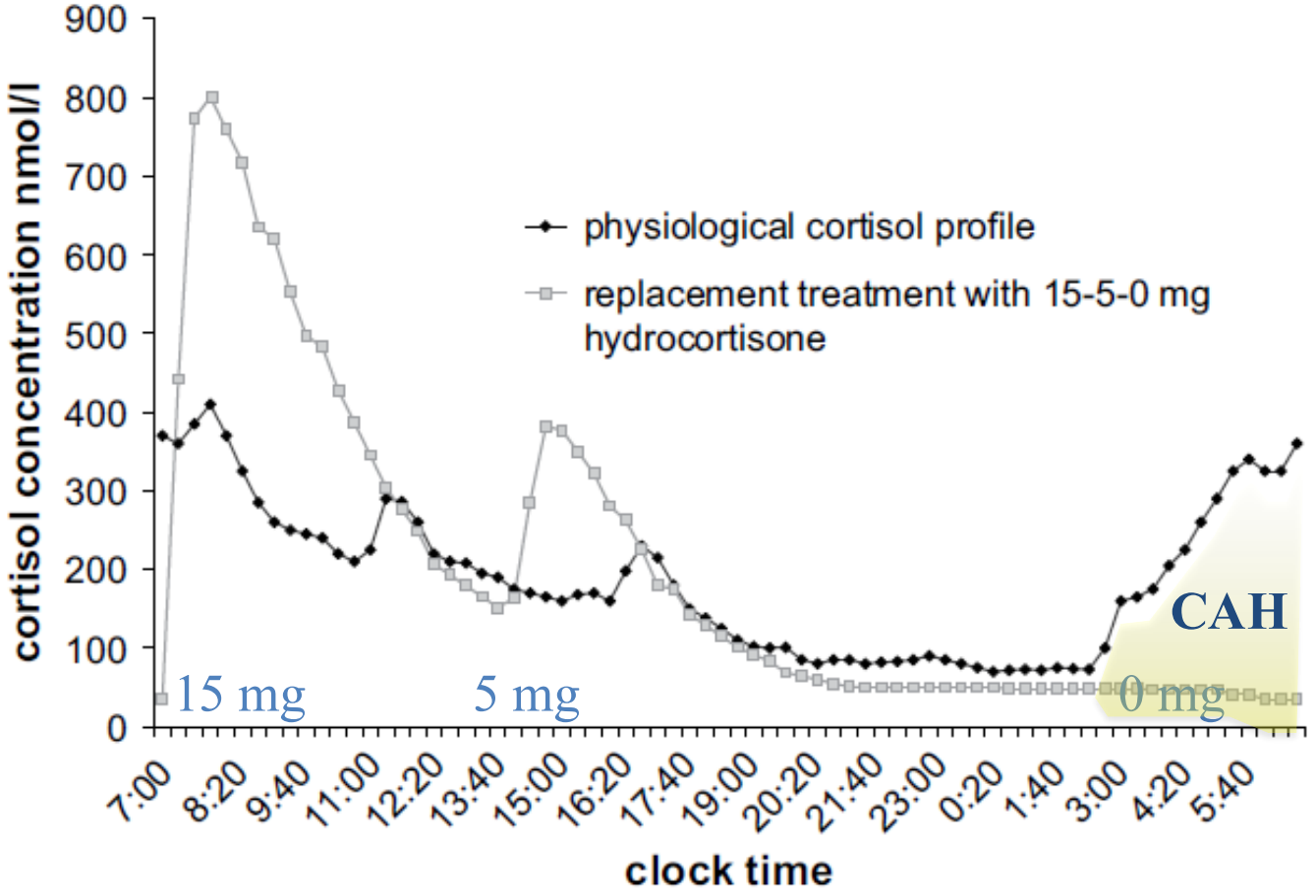


Measure Cortisol every 20 minutes

Peter Hindmarsh, Congenital Adrenal Hyperplasia: A Comprehensive Guide

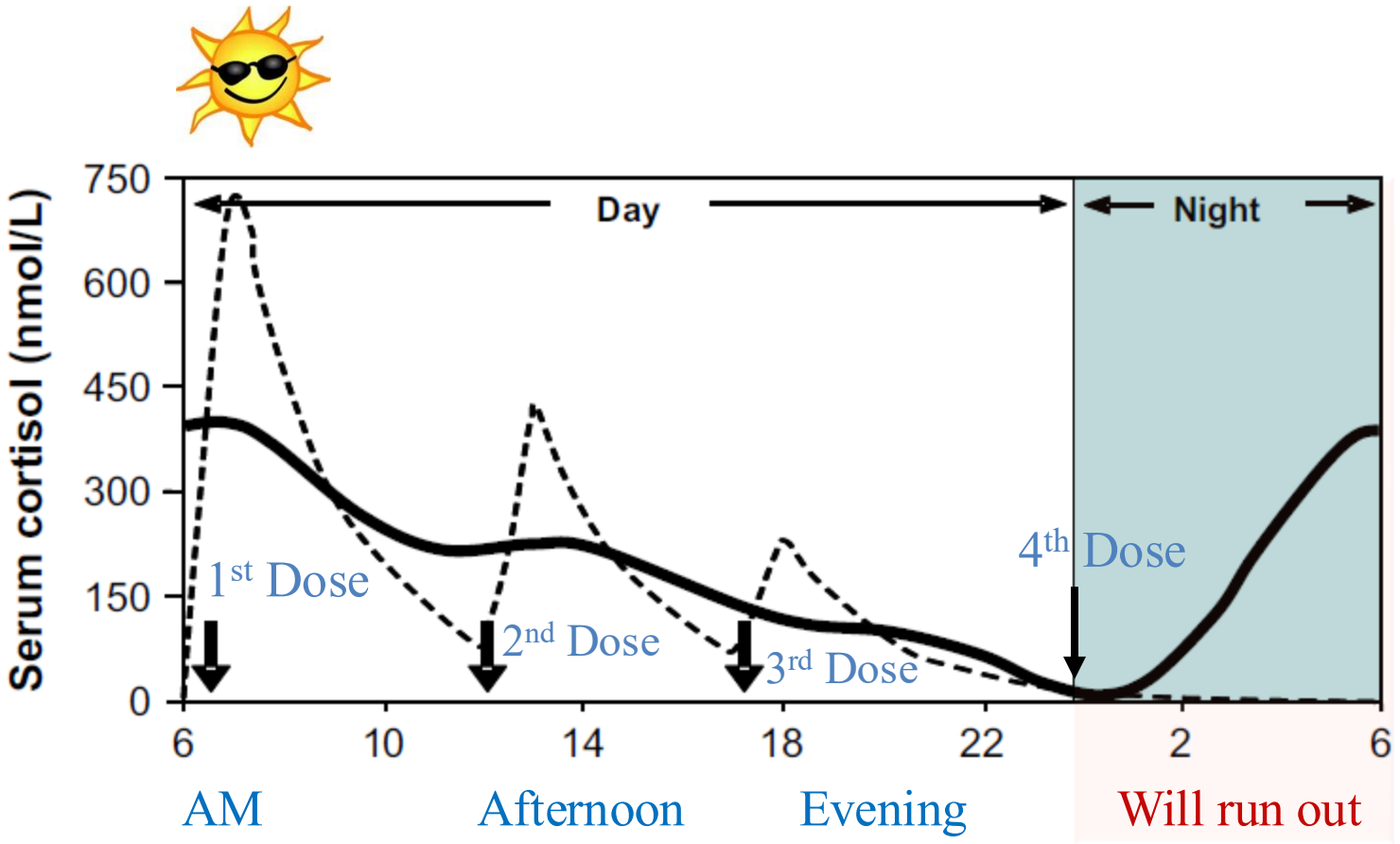
Children's Hospital LOS ANGELES
CENTER FOR ENDOCRINOLOGY, DIABETES AND METABOLISM

HYDROCORTISONE DOSING: BID?



Hahner and Allolio, Best Practice & Research Clinical Endocrinology & Metabolism 2009

HYDROCORTISONE DOSING: TID?

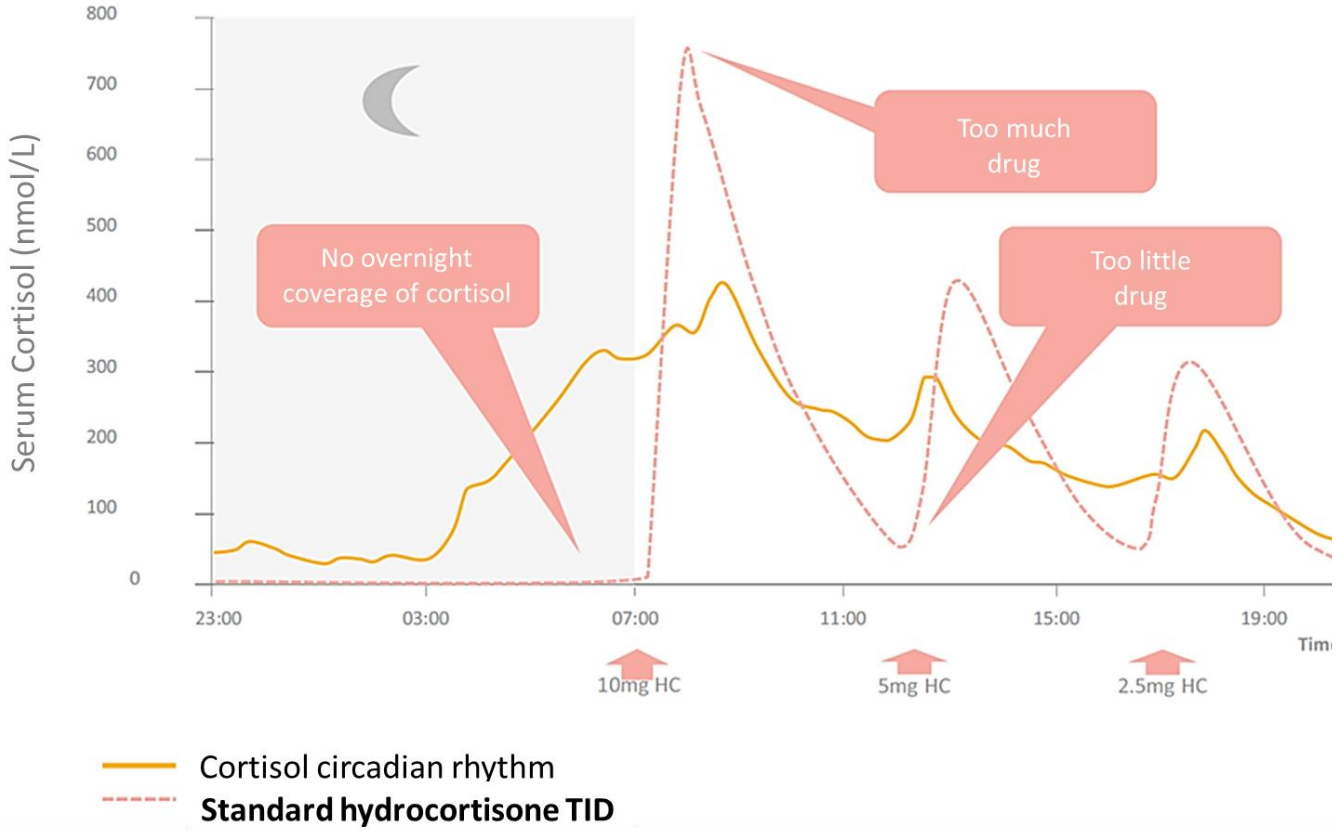


PEAK AM

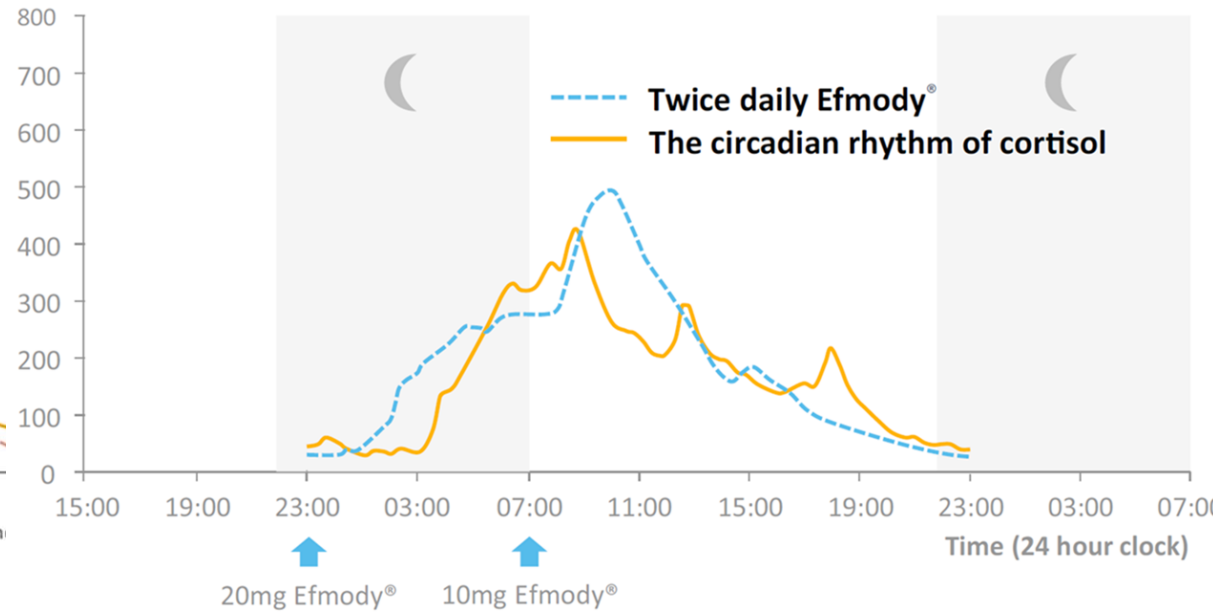
Mah et al. Clinical Endocrinology 2004

Current therapy does not match circadian cortisol secretion

Goal: Mimic cortisol circadian rhythm

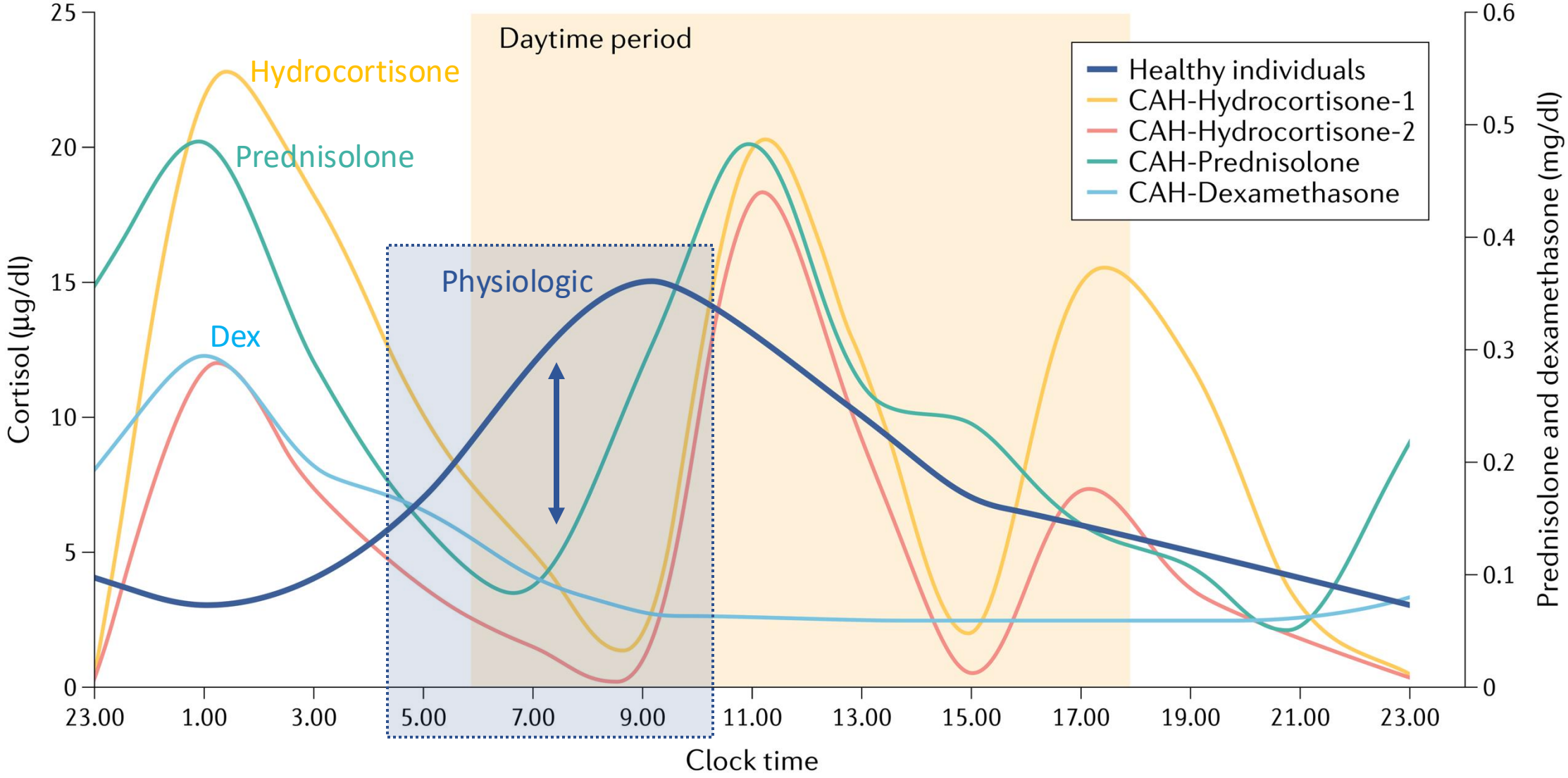


Modified Release-HC (Adults) Phase II-III Trial



Whitaker et al., Drug Deliv Transl Res. 2023

24-h Glucocorticoid Profiles



Mallappa & Merke, Nat Rev Endocrinol, June 2022

EMERGENCY

Guidelines – Adrenal Insufficiency
Journal of Clinical Endocrinology & Metabolism (2016)

SPECIAL FEATURE

Clinical Practice Guideline

Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline

Stefan R. Bornstein (chair), Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, and David J. Torpy*

Objective: This clinical practice guideline addresses the diagnosis and treatment of primary adrenal insufficiency.

Participants: The Task Force included a chair, selected by The Clinical Guidelines Subcommittee of the Endocrine Society, eight additional clinicians experienced with the disease, a methodologist, and a medical writer. The co-sponsoring associations (European Society of Endocrinology and the American Association for Clinical Chemistry) had participating members. The Task Force received no corporate funding or remuneration in connection with this review.

Adrenal Insufficiency Guidelines

Management and prevention of adrenal crisis in patients with PAI

- Patients with suspected adrenal crisis should be treated with an immediate parenteral injection of 100 mg (50 mg/m2 for children) hydrocortisone, followed by appropriate fluid resuscitation and 200 mg (50 –100 mg/m2 for children) of hydrocortisone/24 hours.
- **If hydrocortisone is unavailable, prednisolone as an alternative. Dexamethasone is the least preferred alternative and should only be given if no other glucocorticoid is available.**
- **For the prevention of adrenal crisis, adjust glucocorticoid dose according to severity of illness or magnitude of the stressor.**
- Patient education is recommended for glucocorticoid adjustments in stressful events and adrenal crisis prevention strategies including parenteral self- or lay-administration of emergency glucocorticoids.

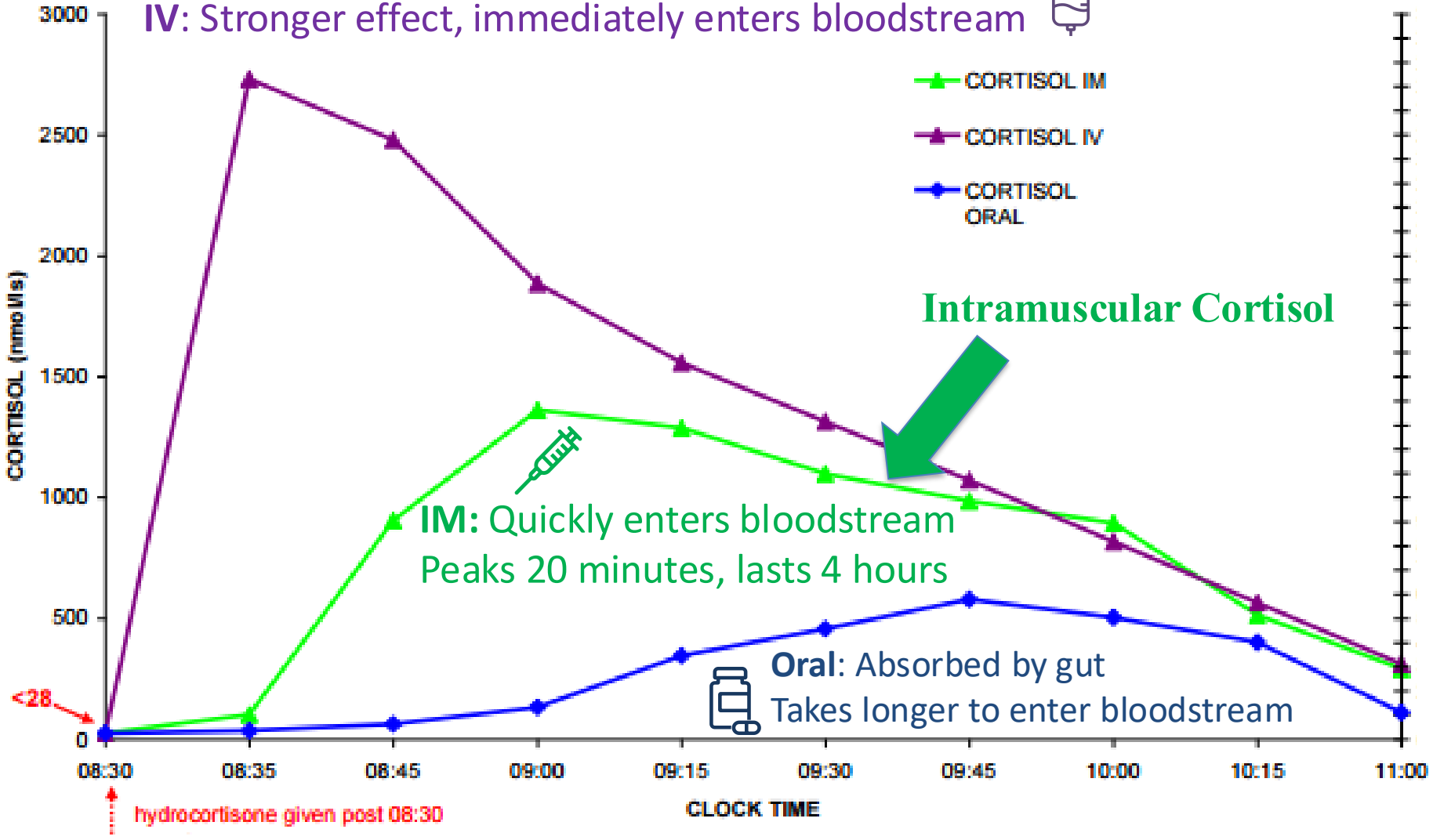
OLDER TEENS & ADULTS: GRAB YOUR SICK DAY BOTTLE OF 20'S

Moderate Illness
= 20 mg tab every 8 hours

Severe Illness
= 20 mg tab every 6 hours

“Give Shot, Go to ER”

IV: Stronger effect, immediately enters bloodstream



Adapted from Peter Hindmarsh

MEDICATION SAFETY ALERT

(EMS PROTOCOLS FOR ADRENAL CRISIS)

Dear EMS Provider:

Adrenal crisis is a life-threatening condition caused by inadequate adrenocortical function leading to impaired physiological responses to stressors such as illness and injury. This deficit can lead to hypotension, hypoglycemia, shock, and death. Immediate intervention can be lifesaving. You may be encountering an adrenal crisis if: the patient takes hydrocortisone, prednisone, dexamethasone, or other glucocorticoids on a regular basis; and/or is having signs/symptoms including: nausea, vomiting, hypotension, and/or altered mental status. ***Patients may carry cards or instructions from their physician for management of adrenal crisis with injectable hydrocortisone; if not, follow dosing recommendations below and contact/inform medical control.***

The following recommended treatment reflects current consensus-based guidelines.[1]

- 2 mg/kg INJECTABLE **HYDROCORTISONE** (as sodium succinate or sodium phosphate) up to a maximum of 100 mg
- Can be given: IM/IV/IO/SC
- General rule: Err on the higher side of a dose range

For suspected or confirmed adrenal crisis, it is imperative to meet the following medication safety conditions:

- **FIRST-LINE MEDICATION**: HYDROCORTISONE
- **RIGHT TIMING**: STAT/IMMEDIATELY
- **RIGHT DOSE**: Weight-based dose and/or Age-based dose / Pediatric vs. Adult

Age-Based Dose Recommendations	Weight-Based Dose Recommendations
• <3 years = 25 mg • 3 to <10 years = 50 mg • 10 years and older = 100 mg	Adult: 100 mg Pediatric: 2 mg/kg* to a maximum of 100 mg *Round up to the nearest 10 mg, e.g., 22.5 kg = 50 mg HYDROCORTISONE Sample pediatric dosing calculations: • 10 kg (22 lb) = 20 mg • 30 kg (66 lb) = 60 mg • 50 kg (110 lb) and up = 100 mg

The following organizations endorse this medication safety alert:

ENDOCRINE SOCIETY

FOUNDATION FOR PRADER-WILLI RESEARCH
Working Toward an Independent Future

PES PEDIATRIC ENDOCRINE SOCIETY

PituitaryNetworkAssociation

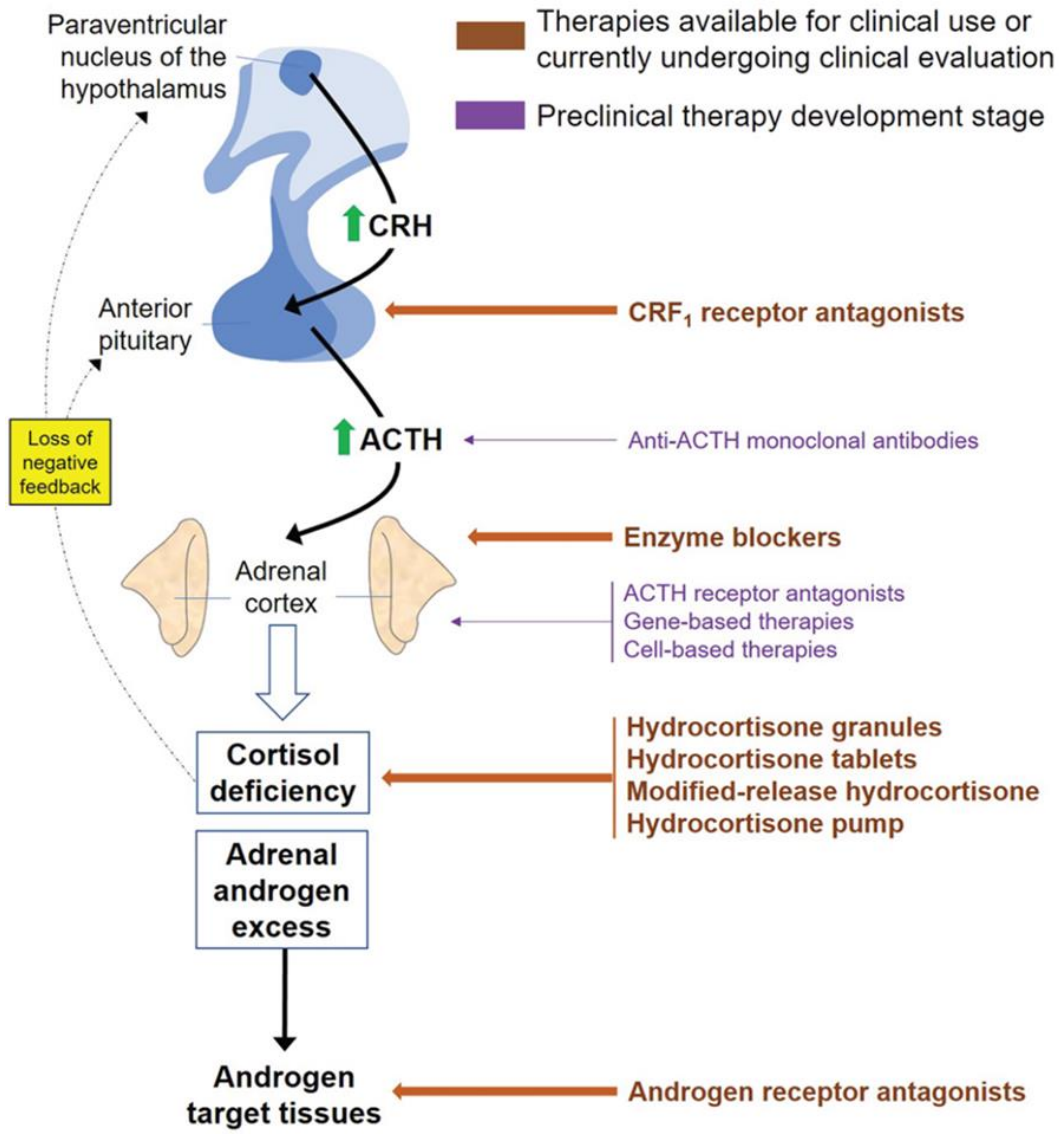
CAEP | ACMU

CPEG GCEP
Canadian Pediatric Endocrine Group
Groupe canadien d'endocrinologie pédiatrique

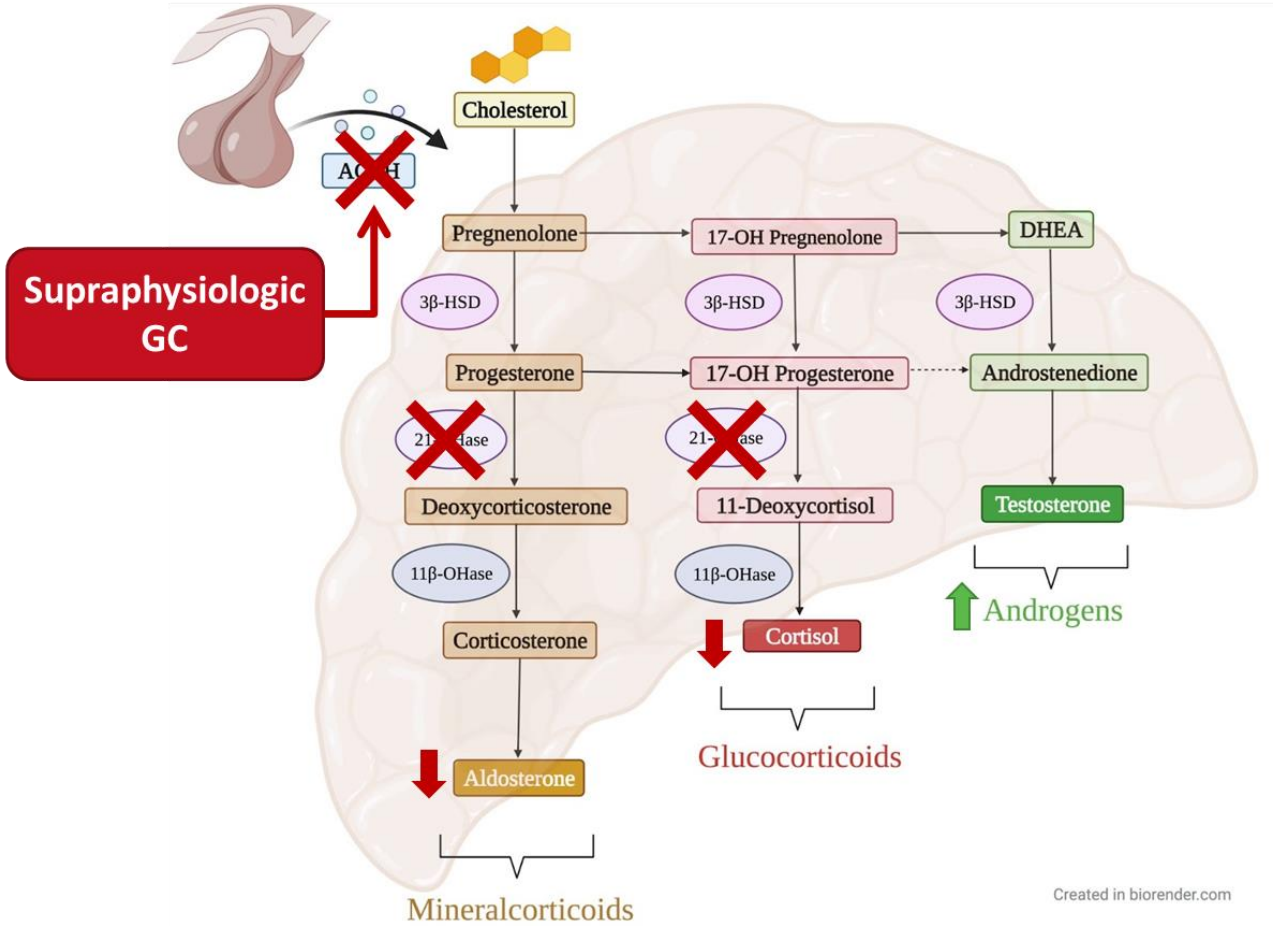
CSEM SCEM
The Canadian Society of Endocrinology and Metabolism
La Société canadienne d'endocrinologie et de métabolisme

CARESFoundation
Centers of Excellence

NOVEL THERAPEUTICS IN CAH



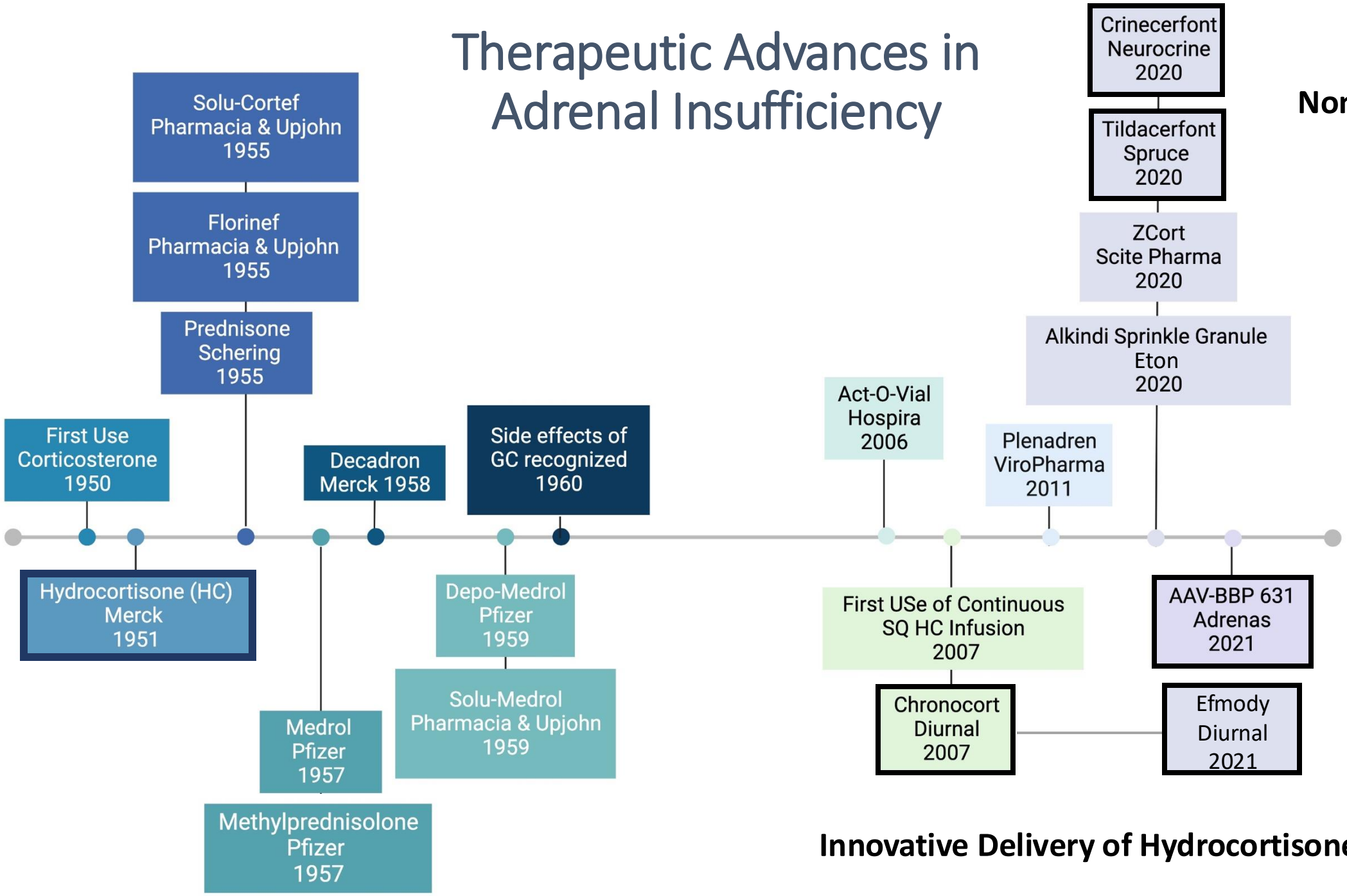
21OHD-CAH Therapeutics: New Approach is Needed

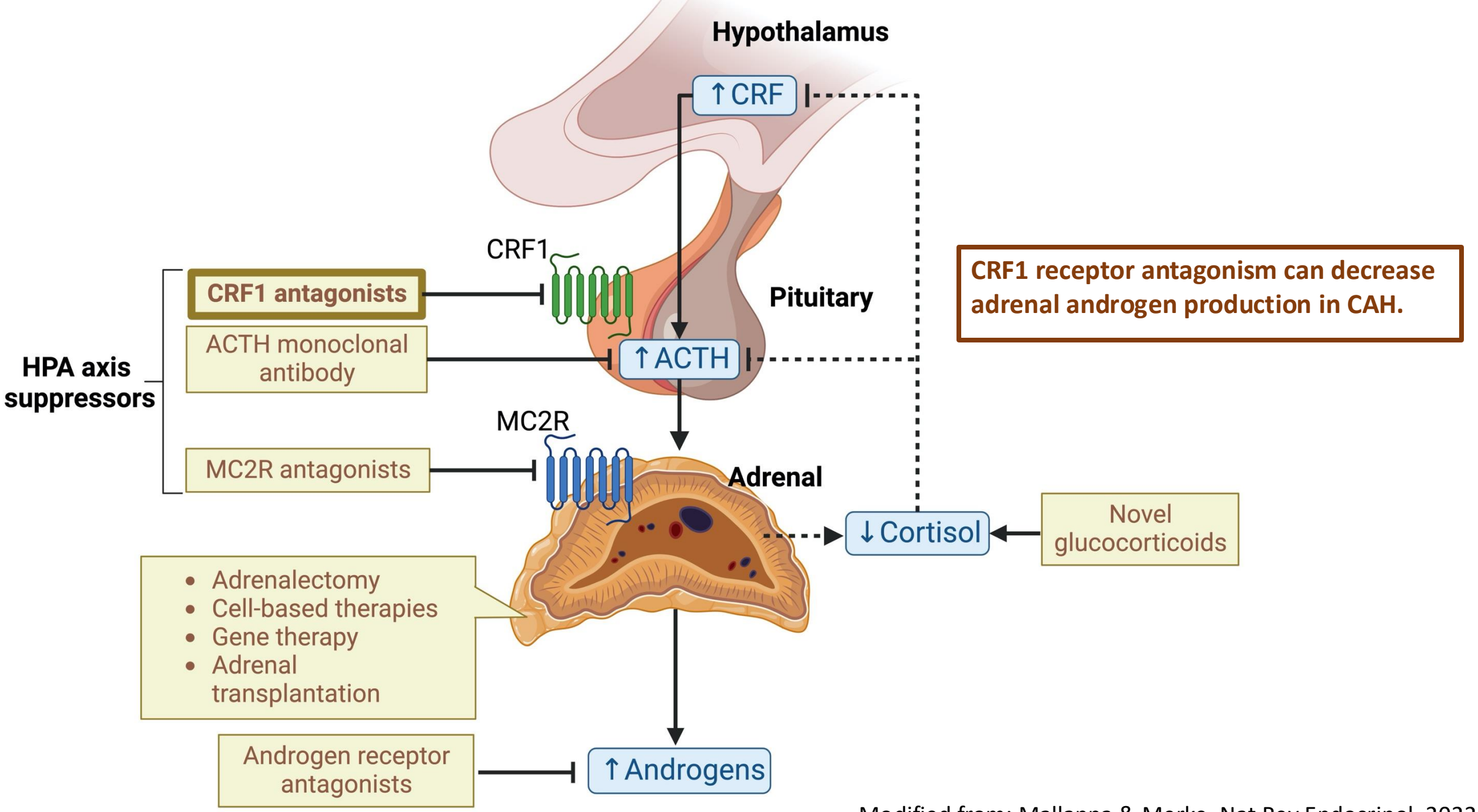


Therapeutic Goals:

- Reduce adrenal androgen excess independent of supraphysiologic GCs
- Decrease GC doses to near-physiologic
- Mimic physiologic circadian cortisol rhythm

Therapeutic Advances in Adrenal Insufficiency





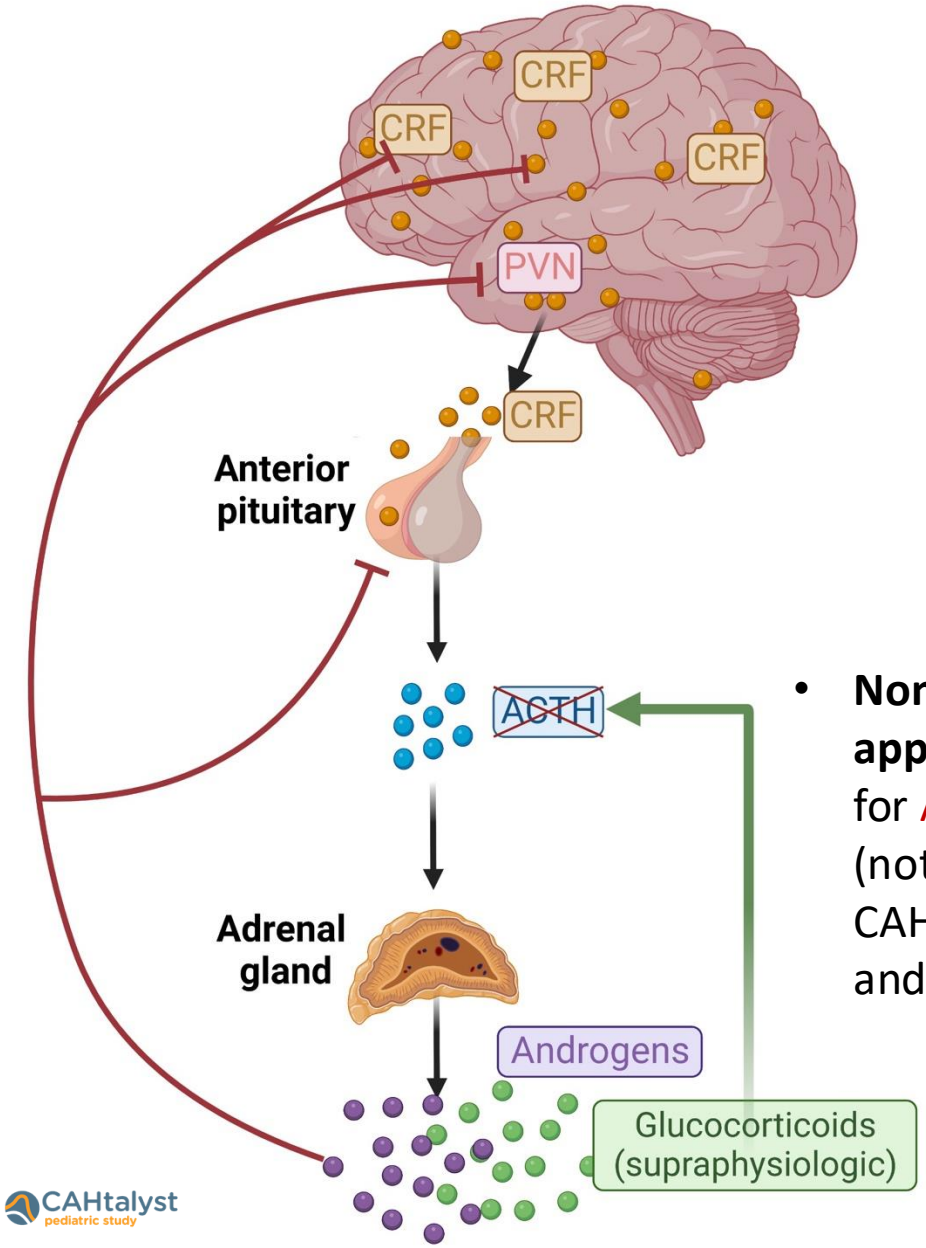
CRF1 receptor antagonism can decrease adrenal androgen production in CAH.

Modified from: Mallappa & Merke, Nat Rev Endocrinol, 2022

CRF1 Receptor Antagonists

<u>CAH due to 21-OHD</u>

Supraphysiologic doses of GCs are commonly required to suppress ACTH and decrease **androgen excess**



- **Non-Glucocorticoid approaches** are needed for ACTH suppression (not a current goal of CAH therapy) and androgen reduction.

Pipeline:

Phase 3, randomized double-blind, placebo-controlled studies in children (2-17y) and adults: crinecerfont

Phase 2b in children (2-17y) and adults: tildacerfont

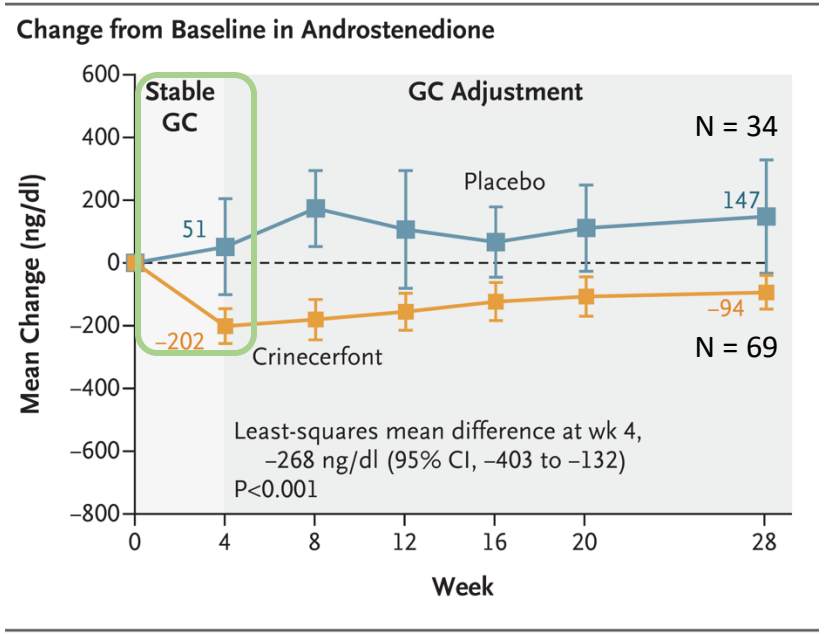
Modified from: Dedic, Chen, Deussing. Curr Mol Pharmacol, 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia

K. Sarafoglou, M.S. Kim, M. Lodish, E.I. Felner, L. Martinerie, N.J. Nokoff, M. Clemente, P.Y. Fechner, M.G. Vogiatzi, P.W. Speiser, R.J. Auchus, G.B.G. Rosales, E. Roberts, G.S. Jeha, R.H. Farber, and J.L. Chan, for the CAHtalyst Pediatric Trial Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

- Crinecerfont effectively reduced elevated androste in pediatric participants with CAH (vs placebo)
- Decrease in the glucocorticoid dose from supraphy physiologic levels while androstenedione control w
- No serious adverse events; well-tolerated overall

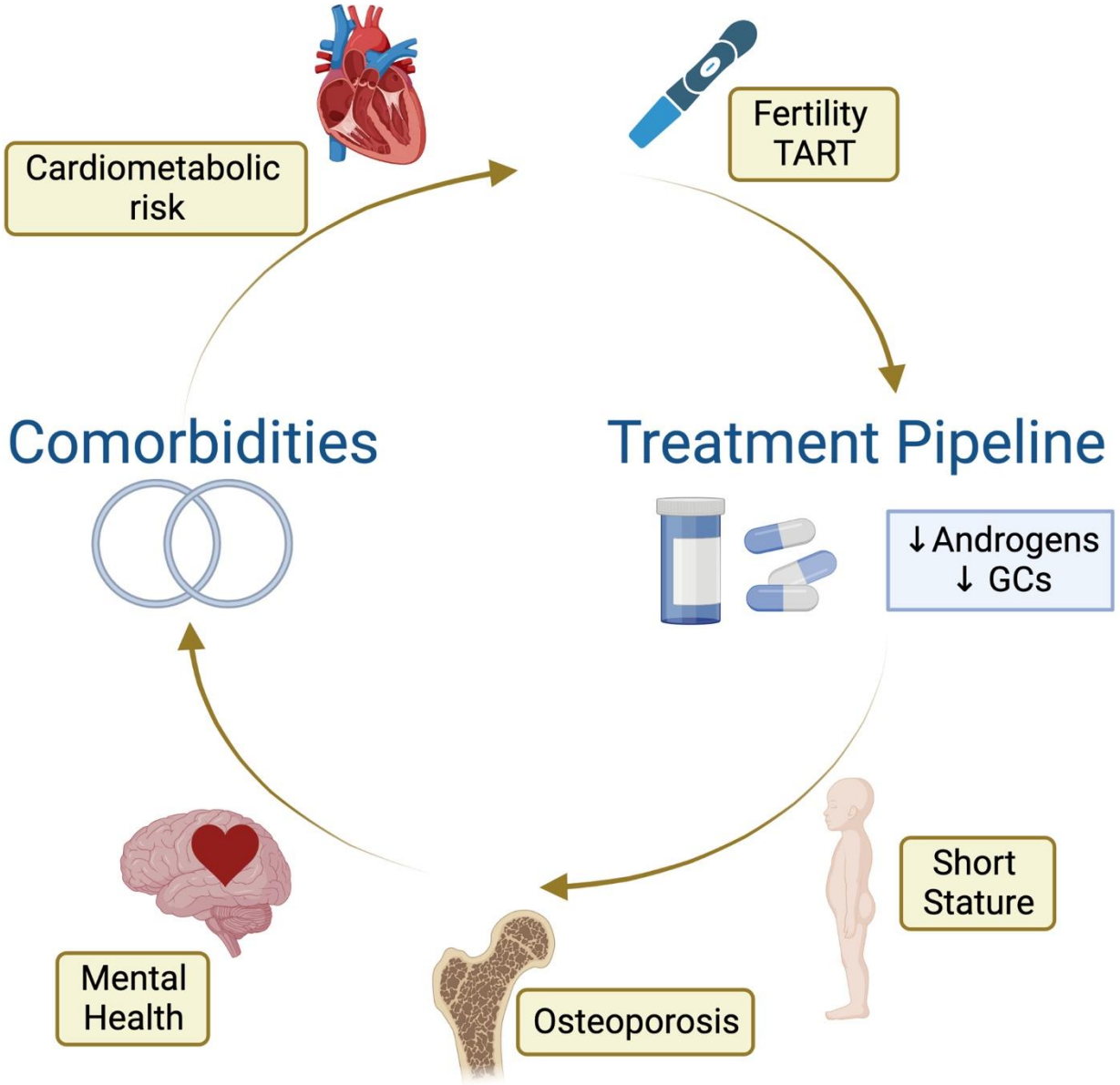
NEJM 2024 Aug

ORIGINAL ARTICLE

Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia

R.J. Auchus, O. Hamidi, R. Pivonello, I. Bancos, G. Russo, S.F. Witchel, A.M. Isidori, P. Rodien, U. Srirangalingam, F.W. Kiefer, H. Falhammar, D.P. Merke, N. Reisch, K. Sarafoglou, G.B. Cutler, Jr., J. Sturgeon, E. Roberts, V.H. Lin, J.L. Chan, and R.H. Farber, for the CAHtalyst Adult Trial Investigators*

CAH Clinical Benefit of Novel Therapies



Created by Biorender

Improved Health Outcomes?

- **Modified Release-HC**

  Associated with clinical benefit (restoration of menses, partner pregnancies, improvement of sperm count in a man with TART)

- **CRF1 Receptor Antagonist**

  Improvement in TART

Longitudinal studies are needed

Post-Test Question 2

A 14 YO girl with classic 21-hydroxylase deficiency returns for evaluation. Menarche occurred at age 12 but periods have been irregular (every 4-10 weeks), and she grooms her facial hair twice weekly.

She has been treated with TID hydrocortisone (15 mg / 5 mg / 5 mg = 16.4 mg/m^2/d) and fludrocortisone 0.1 mg AM for the last year, and she has gained 8 kg over this time. Her BMI is 32 kg/m^2, and she does not want to take more hydrocortisone due to weight gain. She is also bothered by the facial hair and need to groom. Her bone age is 15 4/12 years.

Physical exam shows central obesity, shaved stubble on her chin, and Tanner 5 breasts and pubic hair.

Laboratory data:

Androstenedione 216 ng/dL (7.5 nmol/L); Testosterone 68 ng/dL (2.4 nmol/L);
Sex-Hormone Binding Globulin (SHBG) 35 nmol/L; Fasting glucose 90 mg/dL (5 mmol/L).

Normal electrolytes and plasma renin.

slido

Please download and install the Slido app on all computers you use

Q2b: What additional medication would most effectively lessen the androgen exposure without more glucocorticoid exposure and help to regularize her menses?

ⓘ Start presenting to display the poll results on this slide.

Congenital Adrenal Hyperplasia Across The Lifespan Part 2: Adulthood

Richard J. Auchus, MD, PhD, FACE
The James A. Shayman & Andrea S. Kevrick Professor of Translational Medicine
Division of Metabolism, Endocrinology & Diabetes
Departments of Internal Medicine & Pharmacology
University of Michigan & Ann Arbor VA Medical Center

CONFLICT OF INTEREST DECLARATION – Dr. Richard Auchus

I **DO** have a relationship with for-profit/not-for-profit organizations to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organization(s)	Description of relationship(s)
Any direct financial payments including receipt of honoraria	Neurocrine Biosciences/Diurnal LTD Spruce Biosciences Corcept Therapeutics Crinetics Pharmaceuticals Recordati Rare Diseases Adrenas Therapeutics Mineralys Pharmaceuticals	Contracted Research
Membership on advisory boards or speakers' bureaus	Quest Diagnostics Corcept Therapeutics Xeris Pharmaceuticals Crinetics Pharmaceuticals Novo Nordisk Neurocrine Biosciences/Diurnal LTD Recordati Rare Diseases H Lundbeck A/S Sparrow Pharmaceuticals	Consultant

Passing The Baton

Pre-Test Question 3

- A 24 YO woman with classic 21-hydroxylase deficiency and her male partner are attempting to conceive. Her regimen was increased to hydrocortisone 10-7.5-5 mg with meals and fludrocortisone 0.1 mg/d 3 months ago. Since then, she has had regular monthly menses and unprotected intercourse at least twice weekly, but she is not pregnant.
- Laboratory data: Sodium 138 meq/L; Potassium 4.4 meq/L; Androstenedione 150 ng/dL (5 nmol/L); Testosterone 90 ng/dL (3 nmol/L).
- You add prednisolone 1 mg HS and plan to titrate to goal.
- What laboratory result is your goal?

slido

Please download and install the Slido app on all computers you use

Q3a: What laboratory result is your goal? Lab data:
Sodium 138 meq/L; Potassium 4.4 meq/L; Androstenedione 150 ng/dL (5 nmol/L); Testosterone 90 ng/dL (3 nmol/L).

You add prednisolone 1 mg HS and plan to titrate to goal.

ⓘ Start presenting to display the poll results on this slide.

Pre-Test Question 4

A 27 YO man with classic 21-hydroxylase deficiency is evaluated for infertility. His regimen has been prednisone 7.5 mg AM and fludrocortisone 0.2 mg AM for the last 10 years, and he has received poor follow-up during this time. Physical exam shows no cushingoid features or gynecomastia. He is muscular with a full beard, and his testes are 6 mL bilateral and firm.

Laboratory data:

Sodium 135 meq/L; Potassium 4.8 meq/L; Androstenedione 750 ng/dL (25 nmol/L); Testosterone 300 ng/dL (10 nmol/L); Sex-Hormone Binding Globulin 40 nmol/L; LH <0.1 IU/L; FSH <0.3 IU/L.

slido

Please download and install the Slido app on all computers you use

Q4a: What steroid is primarily suppressing his gonadotropins? Lab data: Sodium 135 meq/L; Potassium 4.8 meq/L; Androstenedione 750 ng/dL (25 nmol/L); Testosterone 300 ng/dL (10 nmol/L); Sex-Hormone Binding Globulin 40 nmol/L; LH <0.1 IU/L; FSH <0.3 IU/L

ⓘ Start presenting to display the poll results on this slide.

Transition vs. Transfer

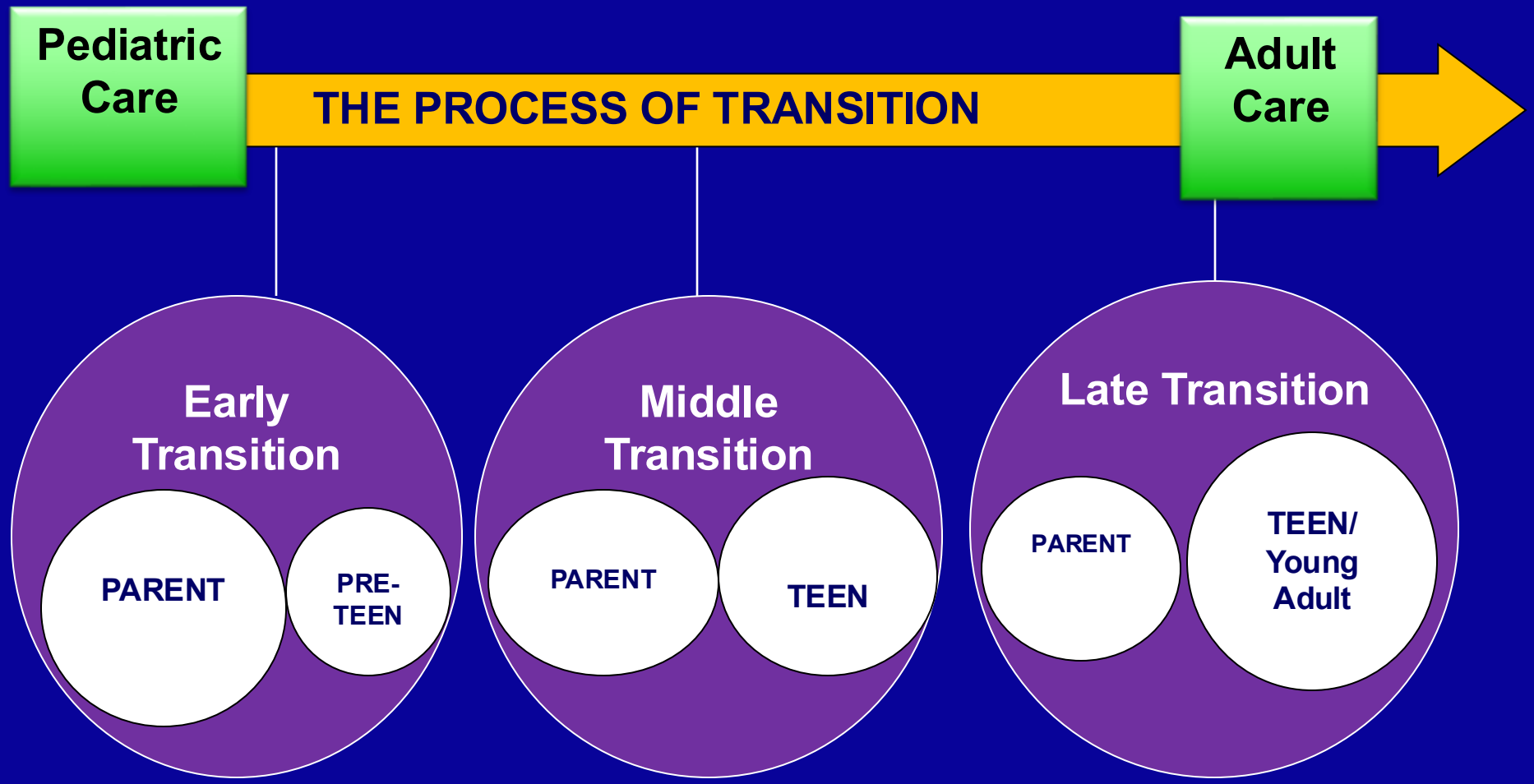
Transition:

"a multi-faceted, active process that attends to the medical, psychosocial, & educational/ vocational needs of adolescents as they move from child- to adult-centered care"

"Transition" = the process of care change
"Transfer" = change of location or provider

Blum RW et al. J Adolesc Health. 1993;14(7):570-6.

The Twofold Process of Transition



Fredericks EM, et al Pediatric Transplantation. 2010

The Transition Process

- Start Early, Phase In Gradually
  - Demonstrates Self-Management Skills
  - Knowledge & Motivation
  - Parents Role Shifts to ‘Consultant’
- Dealing With Healthcare System(s)
- Map Specific Issues To Providers
- Tailor to Individual on the Spectrum
- Ideally Multi-Disciplinary Clinic Access
  - In USA, This Rarely Happens

Team Interventions

- Collaborative, trusting, nonjudgmental relationship
- Visit with adolescent in the absence of parents
- Ask Me 3:
    1. What is my main problem?
    2. What do I need to do?
    3. Why is it important for me to do this?
- Frequent reminders about transition/transfer
- Provide clinical and social support
- Transfer of medical information

#ADULTING 101

Presented by: WellCAT Ambassadors

Car Maintenance | MATC Automotive Technology
Tuesday, September 24 | 6-7:30 p.m.
Lafene Parking Lot

Illness Care at Home | Lafene Health Center
Tuesday, October 1 | 6-7:30 p.m.
Lafene Health Center - Purple Conference Room

Cooking Basics & Food Safety | KSU Dining Services
Tuesday, October 8 | 6-7:30 p.m.
Kramer Dining Center

Conflict Resolution | KSU Conflict Resolution Program
Tuesday, October 22 | 6-7:30 p.m.
Justin Hall 163

Health Insurance | Lafene Health Center
Tuesday, November 5 | 6-7:30 p.m.
Lafene Health Center - Purple Conference Room

Healthy Housing | Sarah Barr, KSU Attorney
Tuesday, November 12 | 6-7:30 p.m.
KSU Union - Wildcat Chambers

Building Good Credit | KSU Powercat Financial
Tuesday, November 19 | 6-7:30 p.m.
KSU Union - Wildcat Chambers

Interview Etiquette | KSU Career Center
Tuesday, December 3 | 6-7:30 p.m.
Berney Family Welcome Center-Davis Theater

WellCAT Ambassadors

Get the scoop!
https://www.k-state.edu/lafene/programs/wellcat-ambassadors/

LAFENE+ HEALTH CENTER
YOUR STUDENT HEALTH RESOURCE

We're Adulting! BINGO

CHECK OFF A SQUARE IF YOU DID THESE IN THE LAST 24 HOURS...

PUT ON PANTS	CLEANED	DIDN'T MURDER YOUR SPOUSE	TOOK A SHOWER	GOT OUT OF BED
SENT A TEXT	BRUSHED YOUR TEETH	DIDN'T SPEND $ ON AMAZON	DIDN'T FALL ASLEEP ON THE COUCH LAST NIGHT	TALKED TO ANOTHER ADULT
FED YOUR KIDS	WENT TO BED BEFORE MIDNIGHT	FREE	ATE REAL FOOD	STEPPED OUTSIDE
DIDN'T DRINK BEFORE 5 PM	WOKE UP BEFORE 10AM	BRUSHED YOUR HAIR	DRANK WATER	DID ANYTHING PRODUCTIVE
WATCHED LESS THAN 8 HRS OF NETFLIX	KNOW WHAT DAY IT IS	KEPT YOUR PET ALIVE	DID SOMETHING CREATIVE	WASHED YOUR HANDS

www.myhomebasedlife.com

Domain-Independent Factors

- Treatment Adherence
  - Cost, Schedules, Titration
- Navigating Medical System Barriers
  - Insurance, Practice, Testing
- Style – Spoiler Alert!!!!
  - Adults Do Not Take Orders From Doctors
  - Adult Doctors Give Up Easier Than Pediatricians
- Burden Of A Chronic Illness
  - Employment & Social Limitations
- In It For The Long Haul

Domain-Specific Factors

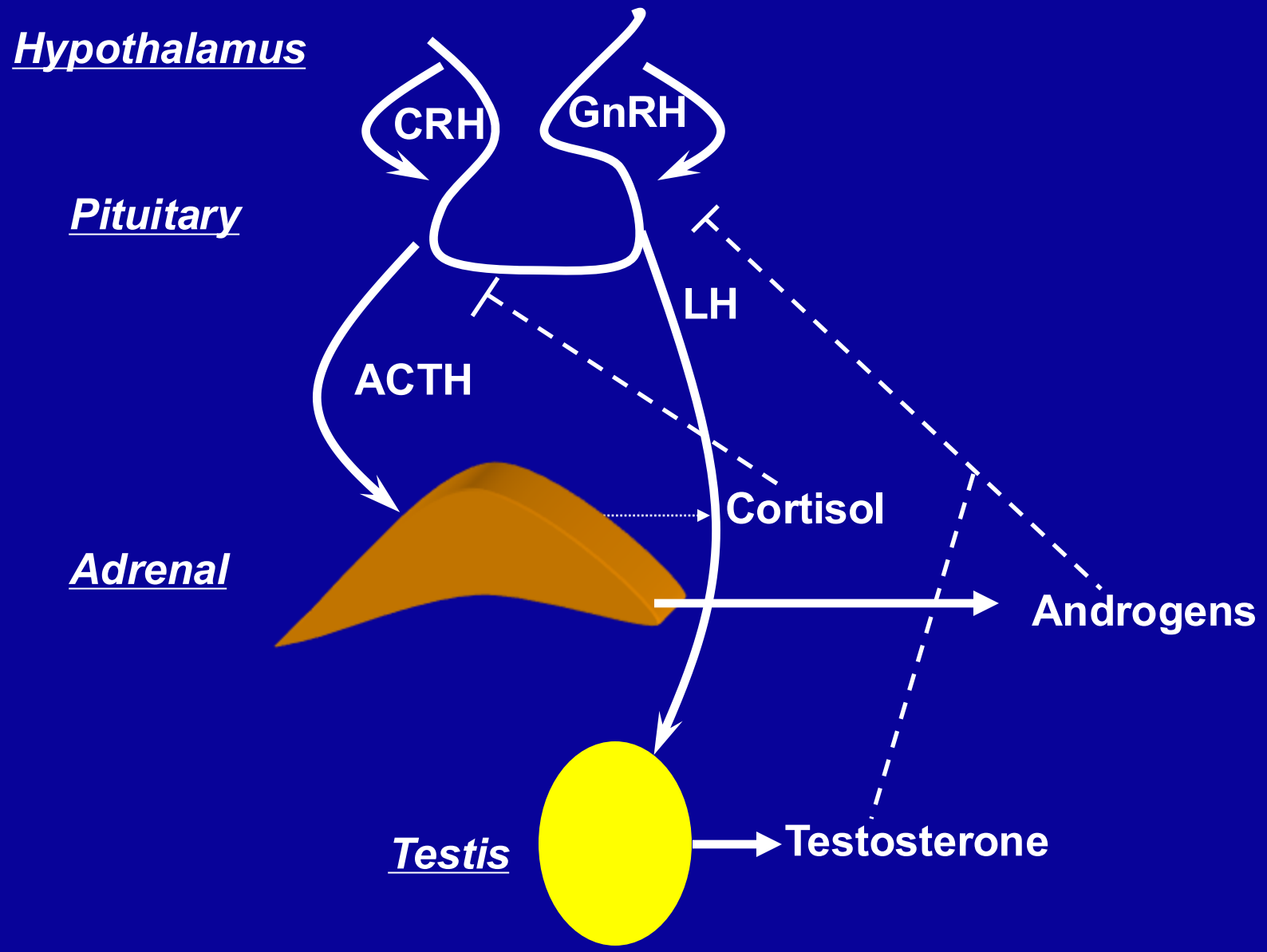
- Hypopituitary/GHD
  - Dose Titration vs Discontinuation; Fertility
- Thyroid
  - Monitoring; Switching Therapy
- Type 1 Diabetes
  - Technology; CHO Counting & Diet Choices
- Adrenal Insufficiency
  - Stress Dosing; Emergency Therapy
- Hypogonadism & DSD
  - Surgery; Fertility; Relationships; Gender

21OHD Adults CaHASE & NIH

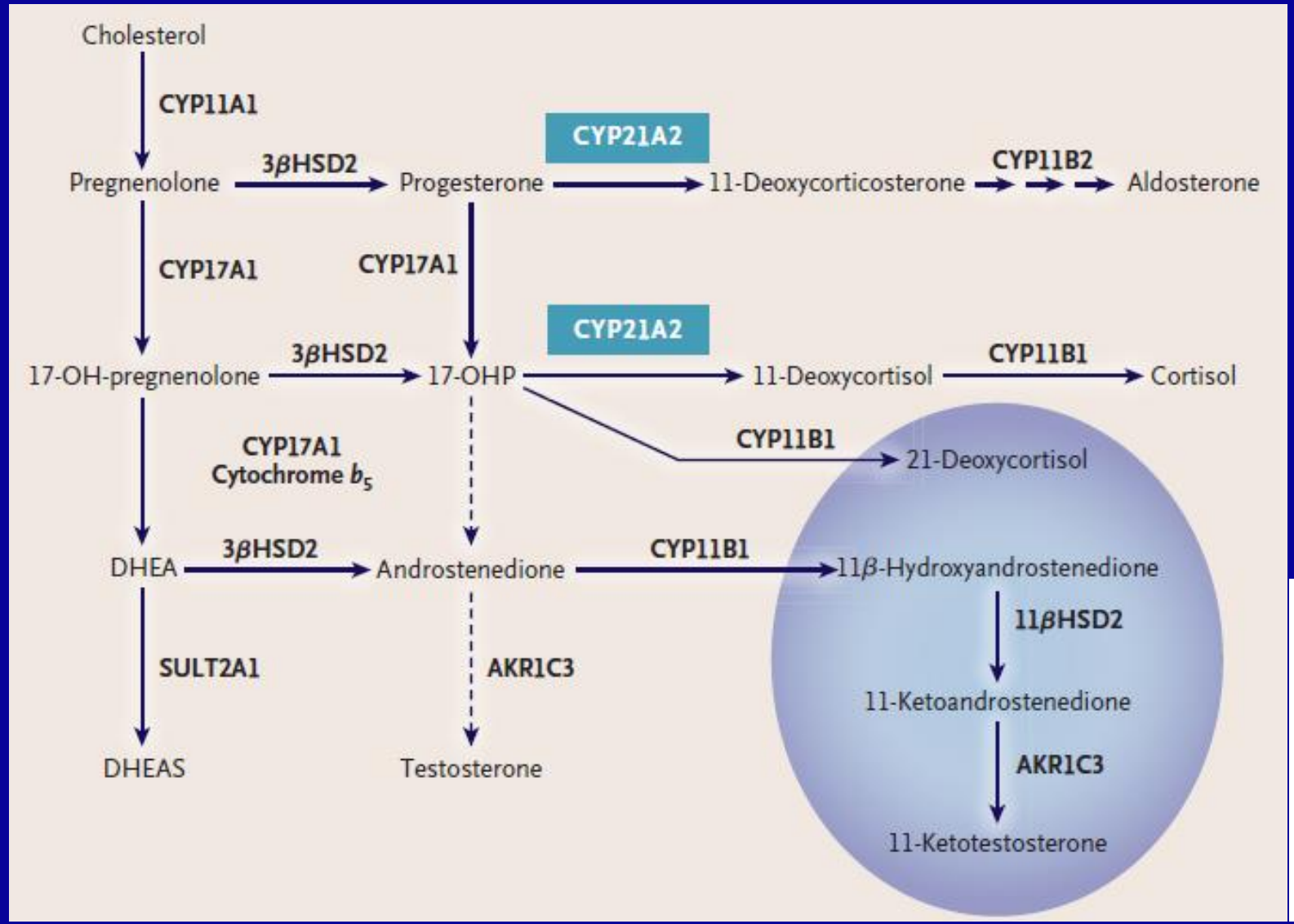
- High or Suppressed Androgens Common
- Obesity Common, One-Third All Groups
- MetS, Insulin Resistance Common
- Elevated BP Common Classic > NCAH
- Low BMD Common 37% Adults
- Adrenal Rests (TART) >50% Boys & Men
- Poor QoL Metrics

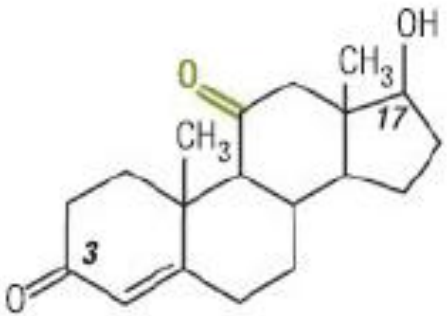
Arlt et al J Clin Endocrinol Metab 2010;95:5110
Finkielstain et al J Clin Endocrinol Metab 2012;97: 4429
Speiser et al J Clin Endocrinol Metab 2018;103:4043
Claahsen-van der Grinten et al Endocr Rev 2022;43:91

Men: 21OHD & Androgens



11-Oxyandrogens



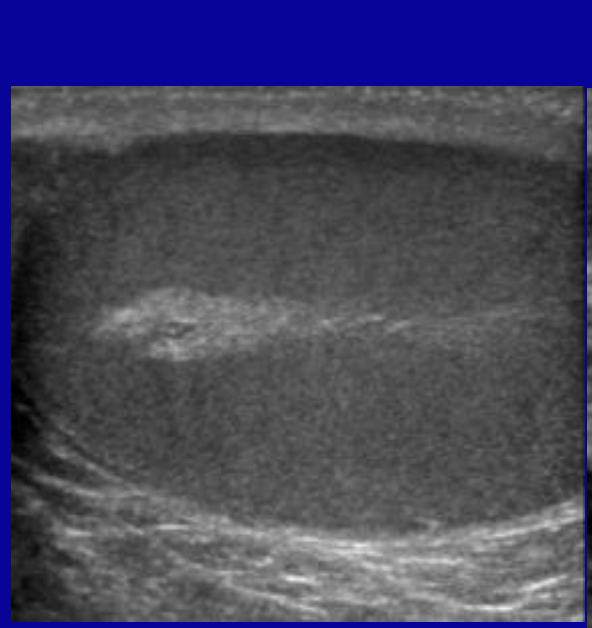


11-Ketotestosterone

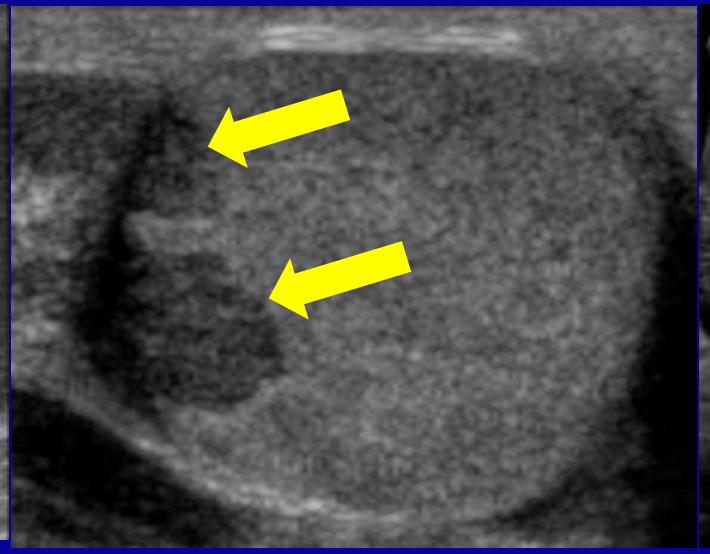
Merke & Auchus N Engl J Med 2020;323:1248
Turcu et al Eur J Endocrinol 2016;174:601

Testicular Adrenal Rest Tumors (TART)

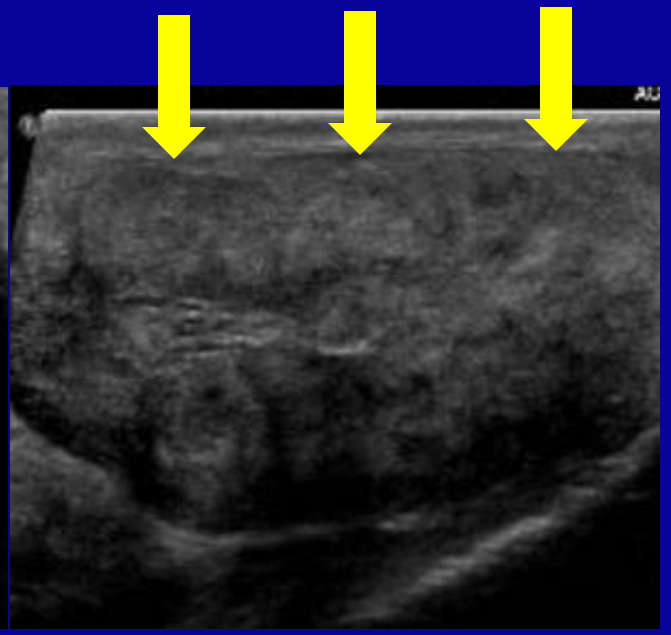
- Tumors <2 cm typically not palpable
- Ultrasound = Modality of choice for detection and monitoring



Normal testis



Small TART surrounding the mediastinum testes



Advanced TART

Adrenal Rests: Treatment

- High-Dose Glucocorticoids
  - Often Shrinks Rest Tissue
  - Variable Effect on Testosterone, Sperm
  - Side Effects of Long-Term Use
- Testis-Sparing Surgery
  - Improves Mass Effect
  - Little Benefit For Testosterone, Sperm
- Up To 3-4 Years' Rx Intensification
- TART, FSH > 35 IU/L Poor Prognosis

Claahsen-van der Grinten et al J Clin Endocrinol Metab 2007;92:612
King et al Clin Endocrinol 2016;84:830

Women: 21OHD & Fertility

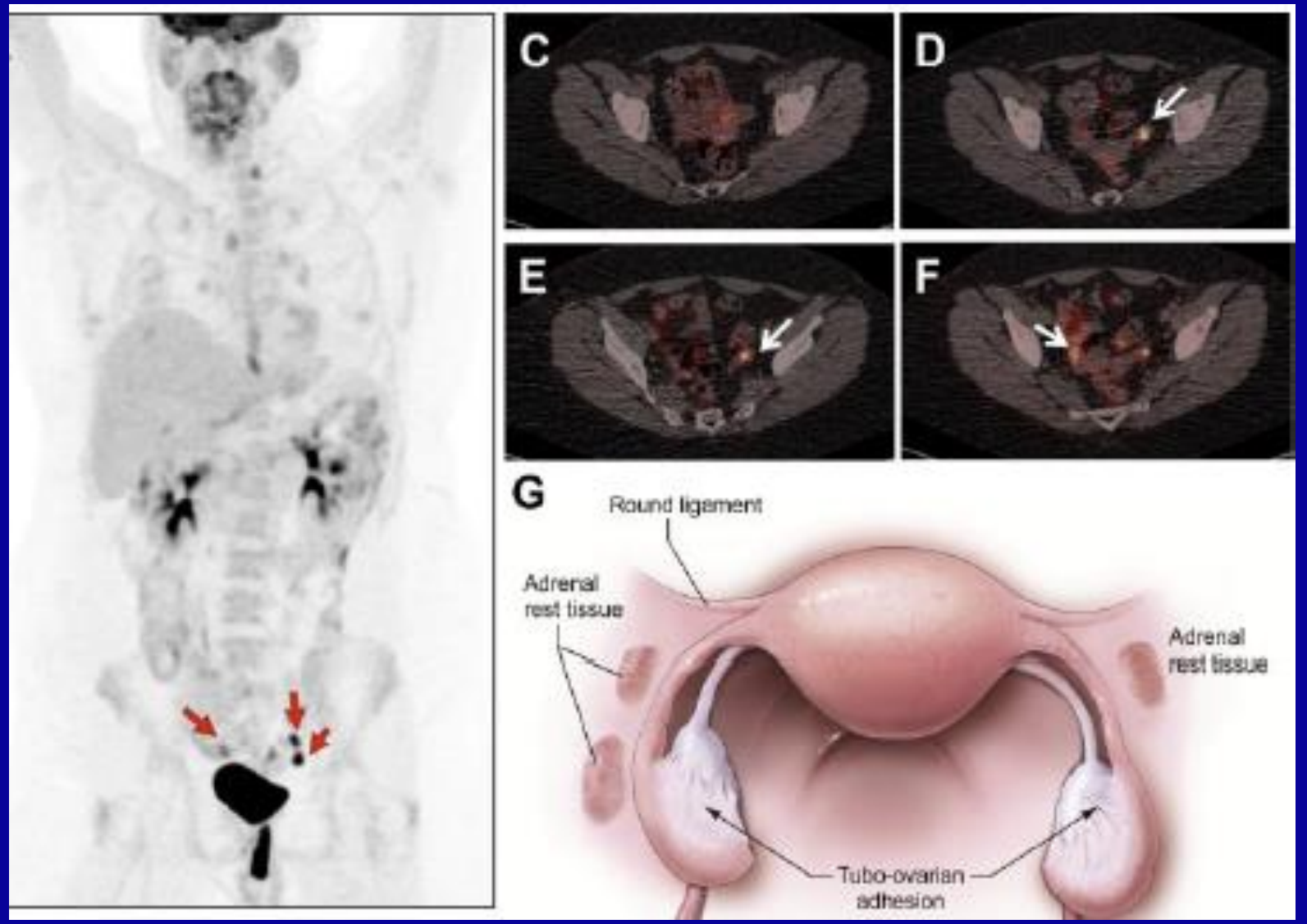
- High Androgens
- High Progesterone
- Anovulation
- Inadequate Introitus
- Vaginal Stenosis/Restenosis

Pregnancy & Classic 21OHD

- Few Attempt Pregnancy (10-25%; Up to 65% Now)
- Pregnancy Rate Normal (>90%)
- Suppress AM Progesterone <0.6 ng/mL
  - Chronic 'Luteal Phase' from Adrenal Progesterone
- Discuss Genotyping Partner, ~1% Carriers
- During Pregnancy
  - Androgens & 17OHP Rise
  - Placenta Protects Fetus From Androgens
- Unilateral/Bilateral Adrenalectomy?

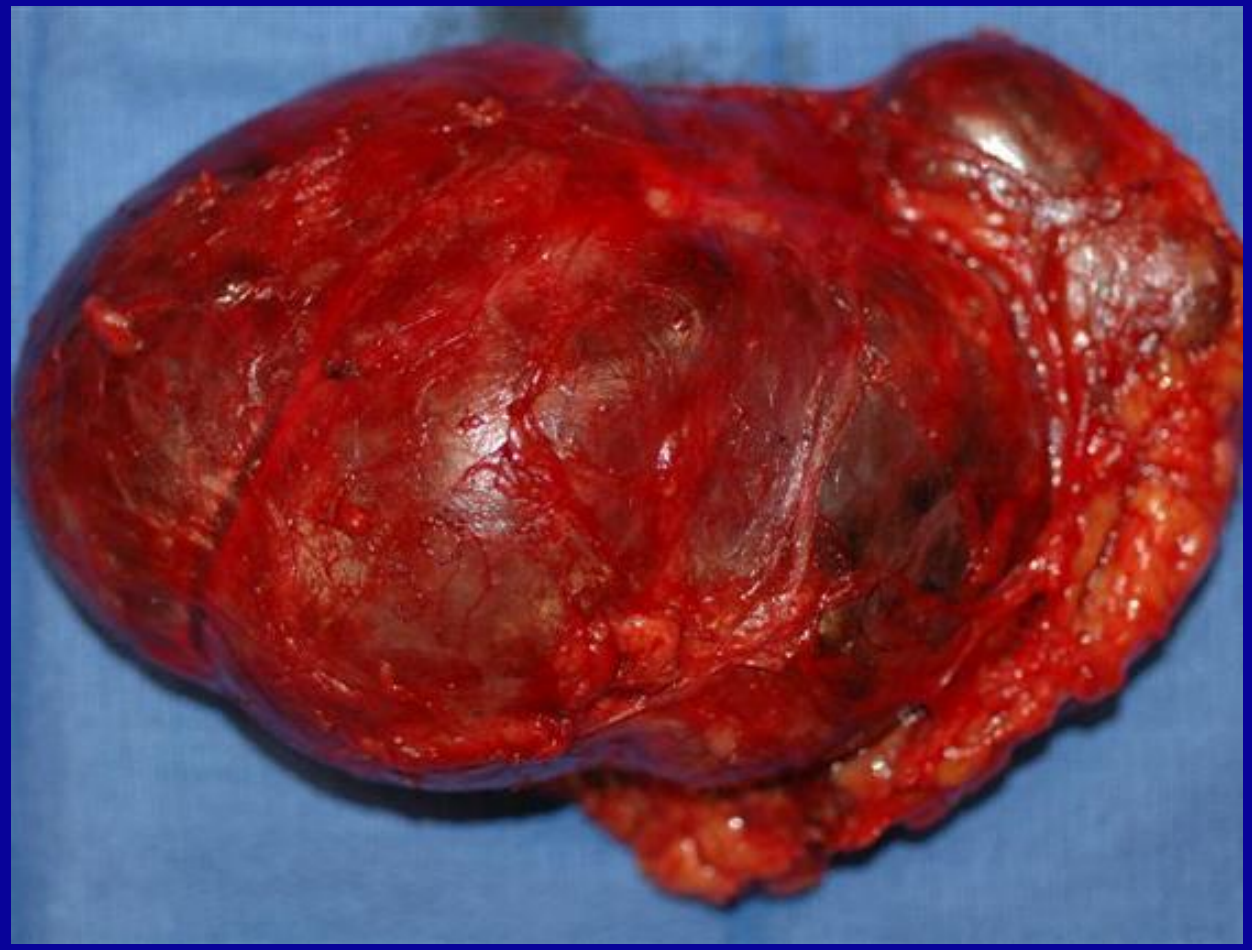
Lo et al J Clin Endocrinol Metab 1999;84:930
Casteràs et al Clin Endocrinol 2009;70:833

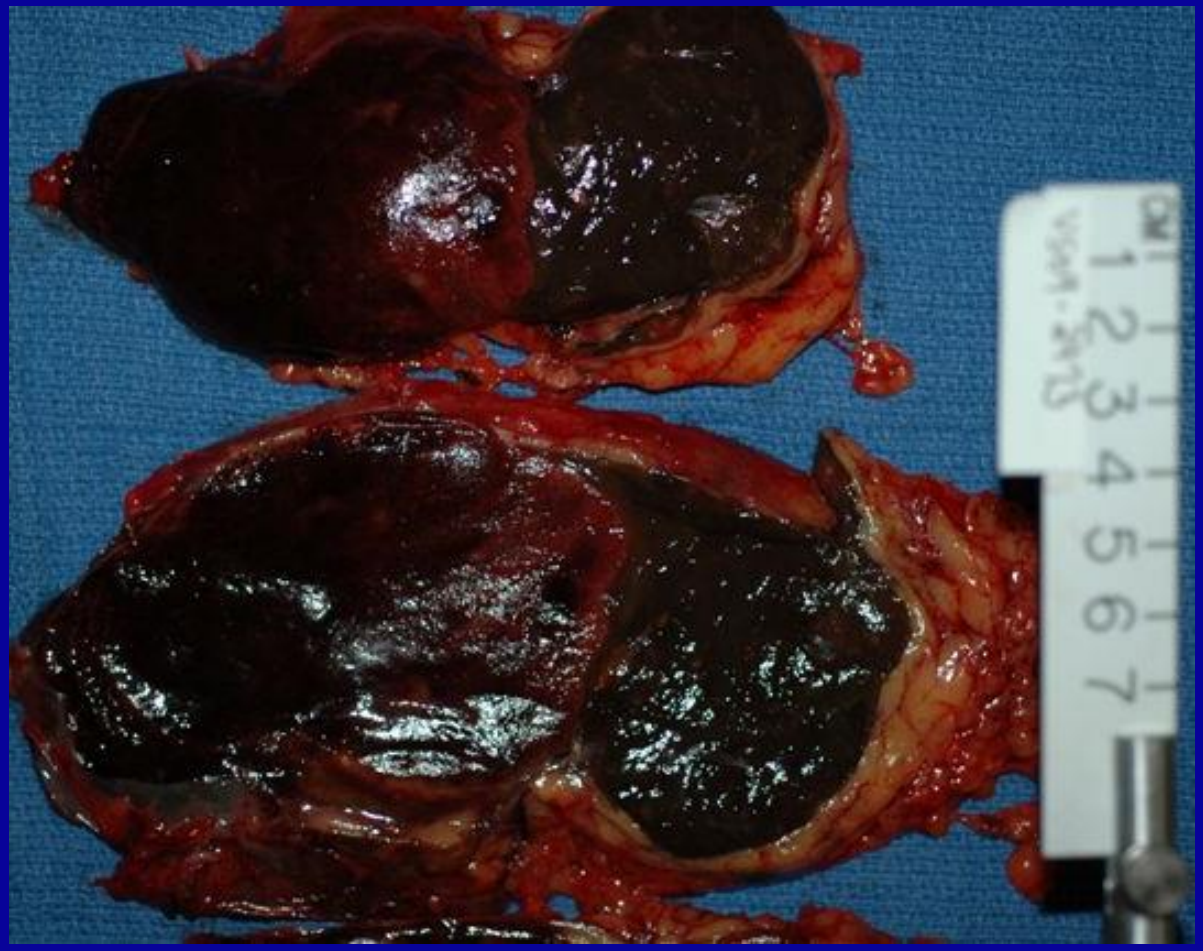
Adrenal Rests After ADX



Crocker et al J Clin Endocrinol Metab 2012;97:E2084

Massive Adrenal Myelolipoma

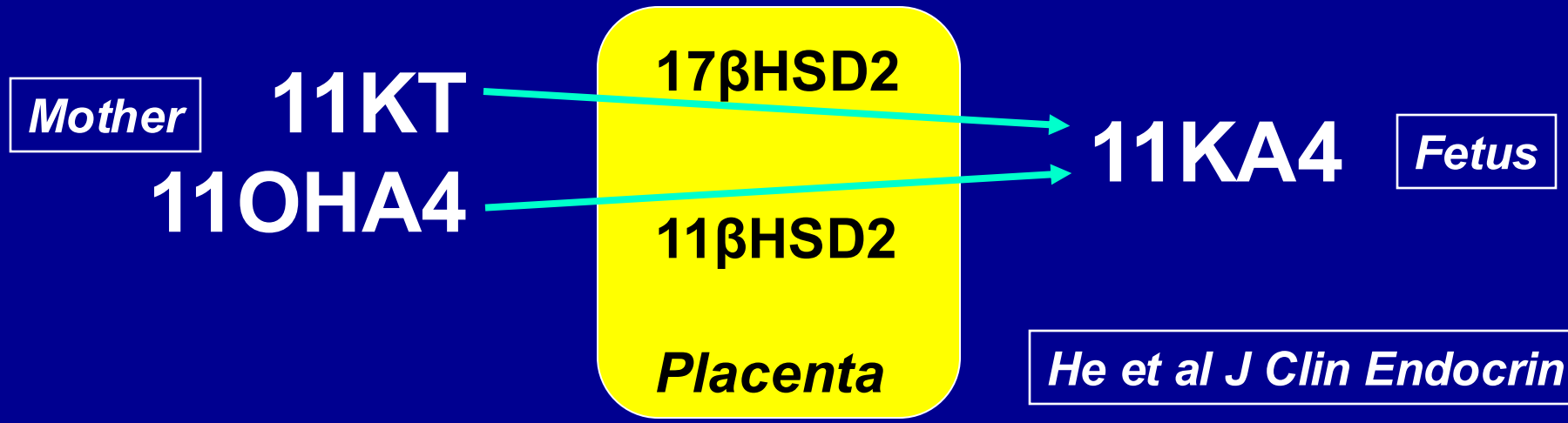




11-Oxyandrogens in Pregnancy

- **MMIP Cohort**
- **Placenta: P450 19A1, 11βHSD2, 17βHSD2**

Steroid (ng/dL)	Maternal First Trimester	Maternal Term	Neonatal Cord Blood
11OHT	4.3 (0.8-14.1)	6.0 (1.1-26.7)	3.5 (0.6-9.3)
11KT	13.6 (2.6-52.6)	18.7 (4.6-64.9)	4.7 (0.01-17.0)
11OHA4	120.3 (26.6-857.9)	264.0 (50.8-2250)	105.3 (16.6-878)
11KA4	27.5 (2.4-338.4)	52.3 (3.7-587.1)	170.7 (11.7-2785)
Sum	~165	~340	~290



He et al J Clin Endocrinol Metab 2022;107:660

Classic 21OHD Case 1

- 25 YO WF Classic 21OHD Trying to Conceive
  - Did Well With Hydrocortisone + OCP Until Age 23
  - Switched To Methylprednisolone 6 mg AM 2 mg HS
- FUV – Labs At Goal, Regular Menses, BUT
  - ++Weight Gain, Purple Striae, Bruising
  - Back to Hydrocortisone 10 mg TID
- 6 Weeks Later: c/o Nausea, Edema, No Menses
  - hCG+
  - Healthy Baby Girl
  - Also Had Second Child-Baby Boy!

Classic 21OHD Case 2: History

- 35 YO AIF Classic 21OHD
  - Fair Control With Hydrocortisone 10+5 mg
  - IVF #1 Age 29: Tubal Pregnancy R
  - IVF #2 Age 30: Tubal Pregnancy L
- First Visit With Me
  - Added 3 mg Prednisolone HS, Fludrocortisone
  - Progesterone 1.6 ng/mL; Change to Prednisolone 5+2 mg
  - Progesterone 0.3 ng/mL
- IVF #3 Age 34: No Pregnancy
- *Cannot Possibly Get Any Worse*

BUT IT GETS WORSE!

- Age 36: One More Attempt
- IVF #4: Implant 3 Embryos
- 6 Weeks Later: hCG 104,000 IU/L
- Sono: Pregnant – With Triplets
- Fetal Reduction? No Way!

Classic 21OHD Case 3: Outcome

- Managed With Hydrocortisone 10 mg TID
  - No Glucose Intolerance
  - No Hypertension
- Stops Work 31 Weeks
- C-Section at 34 Weeks

- 3 Healthy Girls, No NEC or ROP
- Home After <4 Weeks
- Now 3 Preschoolers – Faith, Hope, Grace

Nonclassic 21OHD Presentations

- Children
  - Body Hair & Odor
  - Rapid Growth; Voice & Behavior Changes
- Adolescent Girls & Young Women
  - Facial Hair & Acne
  - Irregular Menstrual Periods
  - Infertility
- >90% Of Females Never Diagnosed
- >99.9% Of Males Never Diagnosed

Nonclassic 21OHD & Fertility

- Ascertainment Rate is Low
- <15% Present For Infertility
- 83-96% Pregnant in 1 Year +/- Treatment
- High Rate of Miscarriage
  - 6-14% With, 20-26% Without Hydrocortisone
- No Data For Infertility or TART in Men
  - Often Stop Treatment After Puberty
- Consider Genotyping Patient, Partner
  - 70% Compound Heterozygous Carriers
- Stress Dosing Only If Suppressed

Bidet et al J Clin Endocrinol Metab 2010;95:1182
Eyal et al Clin Endocrinol 2017;87:552

Long-Term Glucocorticoid Therapy for CAH

"Sophie's Choice"

Physiologic Dosing

- Minimize long-term comorbidities
- Mimic circadian physiology
- Improved compliance

--BUT--

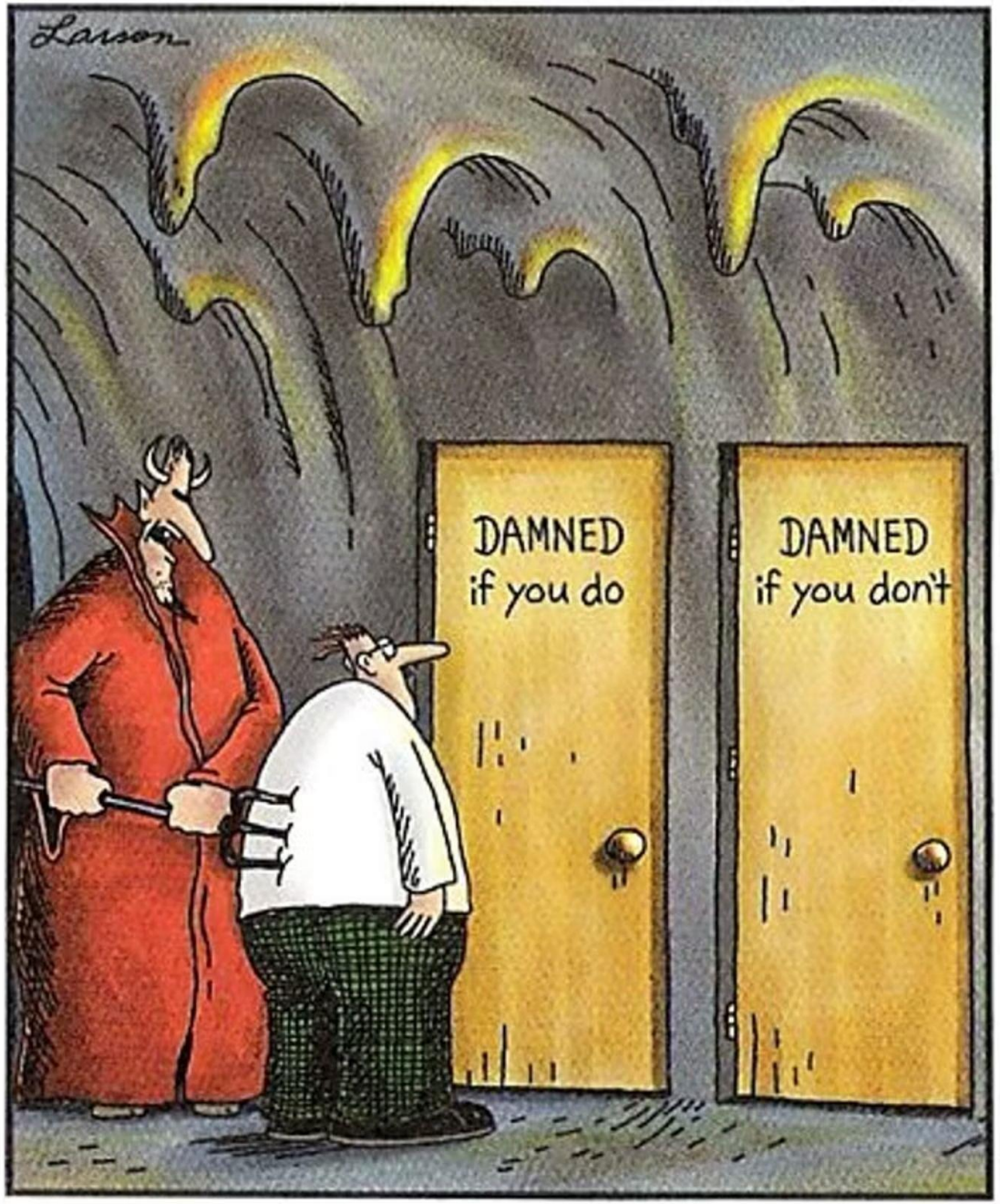
- High androgens
- Sub/infertility
- Tumor development

Supraphysiologic Dosing

- Good androgen control
- Maintain fertility
- Prevent/treat tumor formation (?)

--BUT--

- Weight gain
- Myopathy
- Immunosuppression
- Bone loss
- Glucose intolerance
- Cognitive Dysfunction



"C'mon, c'mon—it's either one or the other."

Glucocorticoid Step Therapy

Step	Drug(s)	Frequency	Total daily dose
1	Hydrocortisone	TID or BID	15-30 mg
2	Hydrocortisone	BID-TID	15-25 mg
	+ Prednisolone	HS	1-2.5 mg
	+ Methylprednisolone	HS	2-4 mg
	+ Dexamethasone	HS	0.1-0.375 mg
3	Prednisolone	BID or TID	5-15 mg
	Methylprednisolone	BID or TID	2-6 mg
	-Typically, 65-75% AM and 25-35% HS		
4	Dexamethasone	QD or BID	0.5-2 mg

Chronic Medication Titration For 21OHD

- Glucocorticoid
  - Cushingoid Features: Bruising, Striae, Skin Thinning, Fat Pads
  - Underdosing: Weigh Loss, Anorexia, PM Fatigue, Androgens
  - Dose Distribution: Trial & Error, Symptoms Improve Post-Dose
  - Exposure: Measure Cortisol 1-2 h Post-Dose (Peak)/Pre-Dose
- Mineralocorticoid
  - Standing BP Most Important
  - Serum K Not High
  - Plasma Renin Not High

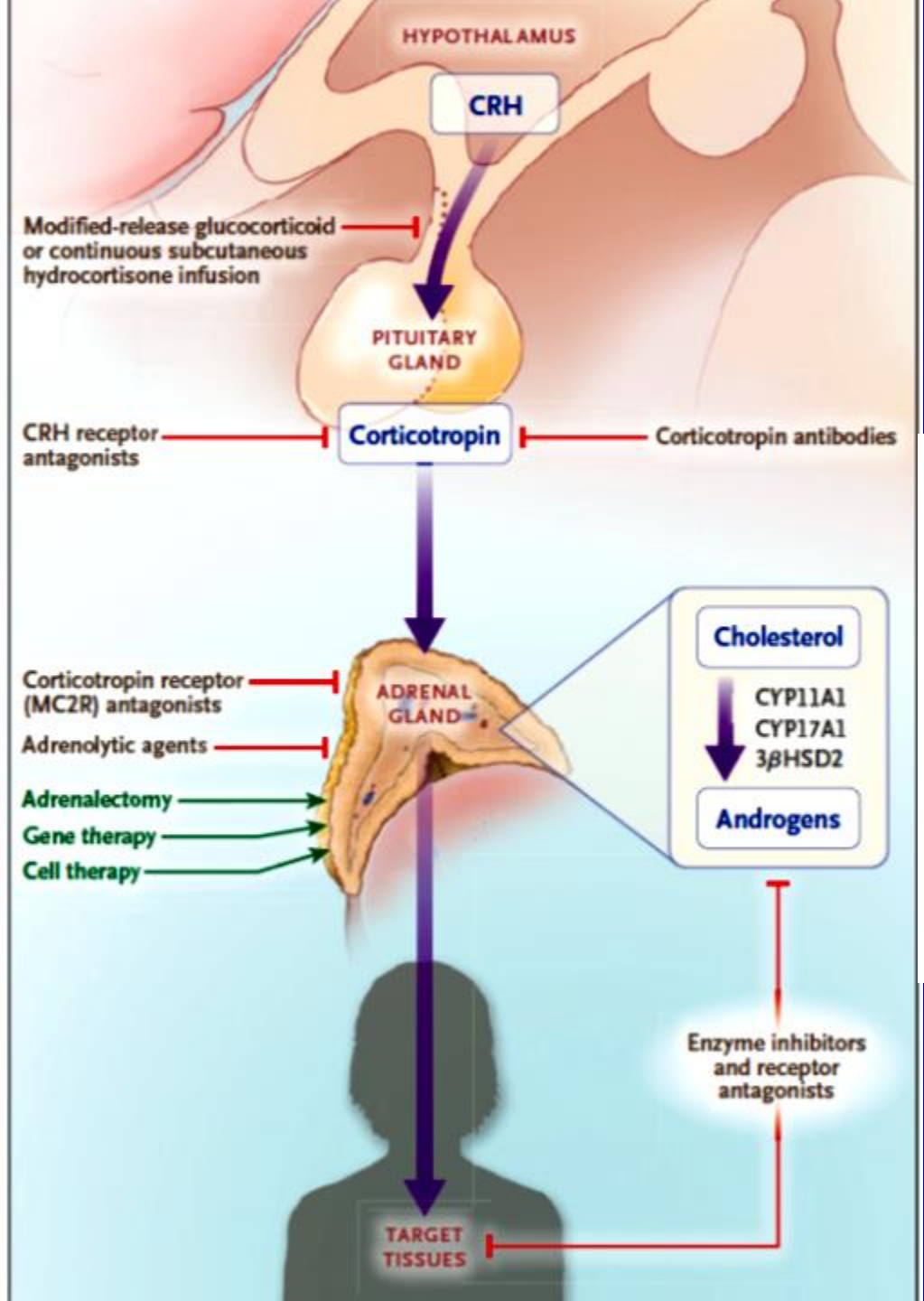
Laboratory Monitoring

Analyte	Physiology	Goals & Comments
Plasma renin	Volume status	Low to normal unless hypertension
Potassium	Mineralocorticoid	Goal is normal
Sodium	Glucocorticoid	Goal is normal
Testosterone (T)	Total androgens	Adrenal + gonadal
Androstenedione	Mostly adrenal	Assess with T
17OHP	Highly variable	Should not be low
SHBG	T binding protein	Estrogen raises
DHEAS	Major adrenal C_{19} Steroid	Low in Classic High in Nonclassic

Laboratory Monitoring

Analyte	Physiology	Goals & Comments
•*Men*		
Gonadotropins	Gonadal axis	Low if adrenal androgen excess
Androstenedione & Testosterone	Adrenal vs gonadal androgen	Ratio should be <0.5
Semen analysis	Fertility	Normal is ideal
•*Women*		
Progesterone	Adrenal & corpus luteum	Normalize for fertility (<0.6 ng/mL) during follicular phase

New Treatments



CSEM SCEM

The Canadian Society of Endocrinology and Metabolism
La Société canadienne d'endocrinologie et de métabolisme

Merke & Auchus N Engl J Med 2020;323:1248

Post-Test Question 3

- A 24 YO woman with classic 21-hydroxylase deficiency and her male partner are attempting to conceive. Her regimen was increased to hydrocortisone 10-7.5-5 mg with meals and fludrocortisone 0.1 mg/d 3 months ago. Since then, she has had regular monthly menses and unprotected intercourse at least twice weekly, but she is not pregnant.
- Laboratory data: Sodium 138 meq/L; Potassium 4.4 meq/L; Androstenedione 150 ng/dL (5 nmol/L); Testosterone 90 ng/dL (3 nmol/L).
- You add prednisolone 1 mg HS and plan to titrate to goal.
- What laboratory result is your goal?

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Q3b: What laboratory result is your goal? Lab data:
Sodium 138 meq/L; Potassium 4.4 meq/L;
Androstenedione 150 ng/dL (5 nmol/L);
Testosterone 90 ng/dL (3 nmol/L).

You add prednisolone 1 mg HS and plan to titrate to goal.

ⓘ Start presenting to display the poll results on this slide.

Post-Test Question 4

A 27 YO man with classic 21-hydroxylase deficiency is evaluated for infertility. His regimen has been prednisone 7.5 mg AM and fludrocortisone 0.2 mg AM for the last 10 years, and he has received poor follow-up during this time. Physical exam shows no cushingoid features or gynecomastia. He is muscular with a full beard, and his testes are 6 mL bilateral and firm.

Laboratory data:

Sodium 135 meq/L; Potassium 4.8 meq/L; Androstenedione 750 ng/dL (25 nmol/L); Testosterone 300 ng/dL (10 nmol/L); Sex-Hormone Binding Globulin 40 nmol/L; LH <0.1 IU/L; FSH <0.3 IU/L.

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Q4b: What steroid is primarily suppressing his gonadotropins? Lab data: Sodium 135 meq/L; Potassium 4.8 meq/L; Androstenedione 750 ng/dL (25 nmol/L); Testosterone 300 ng/dL (10 nmol/L); Sex-Hormone Binding Globulin 40 nmol/L; LH <0.1 IU/L; FSH <0.3 IU/L

ⓘ Start presenting to display the poll results on this slide.

Questions and Answers

Sign in to Slido: Name, Email

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Participant code: #3986602

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