THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

A 31-year-old man with short stature

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Dr. Winer does not have any relevant financial relationships with any commercial interests.

Objectives

- Features of late presentation of a congenital disease
- Management of complications of a poorly treated congenital disease
- Problems with traditional management of a congenital disease

New patient visit

- 31-year-old male self-referred with a history of:
  - Born in Vietnam, moved to US at age 5
  - Pubertal changes started at age 7
  - Full beard by age 10
  - Reached an adult height of 4’7” at age 11
    - Mother: 4’10”
    - Father: 5’2”

Ideas of underlying diagnosis?
What more information would you ask?

Care Everywhere History

- Diagnosed around age 15 with CAH at Swedish Covenant
  - Unclear type of CAH
  - No genetic testing available
- Hypothyroidism diagnosed at same time as CAH
- Noted to have testicular tumor- underwent biopsy with benign path
- Transferred care to Rush
- Started on glucocorticoids and LT4
  - Difficulties with adjusting steroids to control his CAH without overtreatment.
  - Was on Prednisone, dexamethasone and hydrocortisone at varying times

History

Medical:

- CAH
- Hypothyroidism

Surgical:

- Testicular biopsy
- Leg surgeries

Family:

- Mom with hyperthyroidism s/p RAI, now on LT4
- No CAH

Social:

- Moved from Vietnam at age 5
- Goes to gym 1-2x a week

Medications:

- Dexamethasone 0.5mg and 0.25mg PO alternating days
- Florinef 0.1mg daily
- Crestor 10mg daily
- Off LT4

Physical Exam

BP 117/86 | Pulse 82 | Wt 57.6 kg (126 lb)

General: In no acute distress
HEENT: No increased insertions, no proptosis.
Neck: no thyromegaly
Cardiovascular: Regular rate and rhythm
Pulmonary: clear to auscultation bilaterally
Abdominal: Abdomen is soft and flat, **central adiposity**
Musculoskeletal: Spine without step offs, no edema
Skin: no diaphoresis, **purplish abdominal striae**
GU: **Testes: Long axis R 3.5 cm L 3 cm, both firm and irregular**
Neurological: No weakness, 2+ patellar reflexes

Lab and Treatment History

	12/2015
17-HYDROXY PROGESTERONE (<220)	8346
ALDOSTERONE (<21)	
RENIN (0.25-5.82)	20.93
Na	135
K	4.6
Total Testosterone (240 - 950 ng/dL)	115
ACTH (<52 pg/mL)	
Therapy adjustments before labs	HCT 25 BID, Florinef 0.05 BID

Guidelines

Drug	Recommended total daily dose	Divided dosing frequency (times daily)
Children		
Hydrocortisone	10-15 mg/m^2	3-4
Fludrocortisone	0.05-0.2 mg	1-2
Sodium chloride supplements	1-2 g (17-24 mEq/day) in infancy	Several
Adults		
Glucocorticoids		
Hydrocortisone	15-25 mg	2-3
Prednisone	5-7.5 mg	2
Prednisolone	4-6 mg	2
Methylprednisolone	4-6 mg	2
Modified-release hydrocortisone (Plenadren®)	15-25 mg	No published data in CAH patients, clinical experience shows that in addition to the morning dose a second GC dose is required in the evening
Modified- and delayed-release hydrocortisone (Chronocort®)[a]	15-25 mg	2 (2/3 of dose at 2300 and 1/3 of dose at 0700)[a]
Dexamethasone[b]	0.25-0.5 mg	1
Fludrocortisone	0.05-0.2 mg	1

[a] Not yet launched, currently only available within the extension phase of the phase III study.
[b] Avoid if possible or limit to a short time. Adapted from Speiser et al. (133).

Guidelines

Table 5.
Utility of Various Analytes for Monitoring CAH Treatment

Patients	Analyte	Physiology	Goals and Comments
All ages	Plasma renin	Volume status	Low to normal unless hypertensive
	Potassium	MC replacement	Goal is normal
	Sodium	GC and MC replacement	Goal is normal
	Testosterone	Total androgens	Goal is at or near normal
	Androstenedione	Mostly adrenal origin	Goal is at or near normal
	Sex hormone–binding globulin	Testosterone-binding protein	For calculation of free and bioavailable testosterone
	17OHP	Variable	Normal values indicate overtreatment
Men	Testosterone	Adrenal or gonadal origin	Interpret abnormal values in context of gonadotropins and androstenedione levels
	Gonadotropins	Gonadal axis status	Low indicates poor control
	Androstenedione	Mainly adrenal	Goal is <0.5× testosterone
	Semen analysis	Fertility	Goal is normal
Women	Follicular-phase progesterone	Mainly adrenal origin when elevated	Goal is <0.6 ng/mL (<2 nmol/L) for women trying to conceive

(Speiser, P et al, 2010)

Lab and Treatment History

	4/2017
17-HYDROXY PROGESTERONE (<220)	245
ALDOSTERONE (<21)	
RENIN (0.25-5.82)	22.23
Na	139
K	4.0
Total Testosterone (240 - 950 ng/dL)	
ACTH (<52 pg/mL)	
Therapy adjustments after labs	Dex 0.5mg Florinef 0.1mg daily

What should we do?

How does the glucocorticoid impact care in CAH?

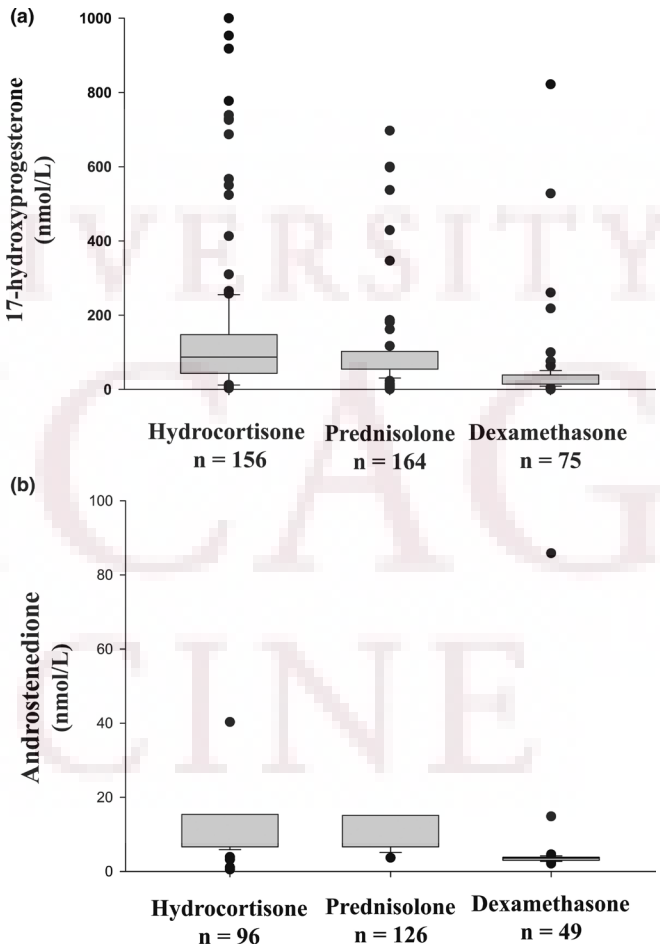
Glucocorticoid choice in CAH

Glucocorticoid Regimens in the Treatment of Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis

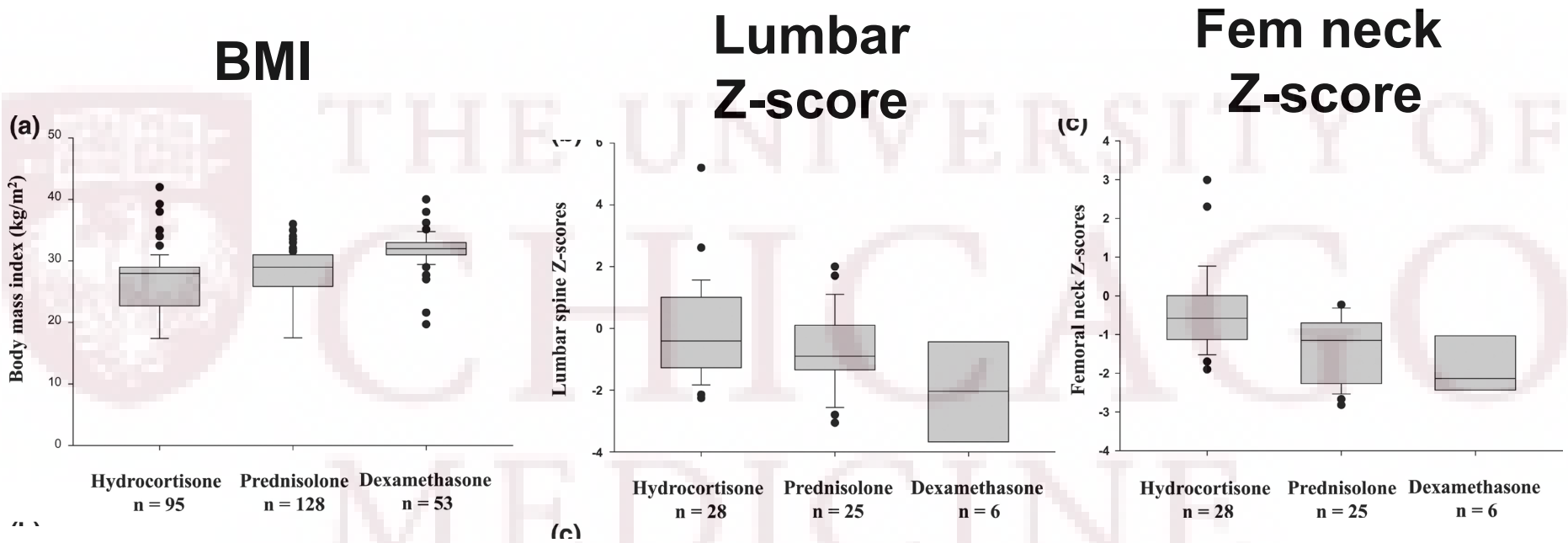
Emma Whittle ✉, Henrik Falhammar

Journal of the Endocrine Society, Volume 3, Issue 6, June 2019, Pages 1227–1245,
https://doi.org/10.1210/js.2019-00136
Published: 18 April 2019 **Article history** ▾

- Meta-analysis of 23 studies
- Dexamethasone had the highest degree of HPA suppression
- HCT and Pred were similar



Glucocorticoid choice in CAH



Guidelines: get a BMD every 3-5 years.

Our patient Z-scores: Spine -1.4, Fem Neck -2.7

(Whittle, E et al, 2019)

Glucocorticoid choice in CAH

Steroid	Clinical indication	Pros	Cons
Hydrocortisone	Preferred option for GC replacement.	Best long-term outcome with regard to metabolic, cardiovascular, and bone health	Short half-life. Needs to be given 3 times daily. Adrenal androgen suppression overnight may escape.
Prednisolone (Prednisone)	Might be a preferred option for regulation of menstrual cycles or fertility induction, or if patient adherence is poor with thrice daily hydrocortisone	Longer half-life, twice daily regimen. Potentially better patient adherence compared with 3 times daily regimen	Potential higher rate of adverse effects on metabolic, cardiovascular, and bone health compared with hydrocortisone
Dexamethasone	Fertility induction TART treatment	Strong adrenal suppressive effect, longest half-life, once daily regimen often possible	Highest rate of adverse effects on metabolism, bone health. Traverses placenta barrier

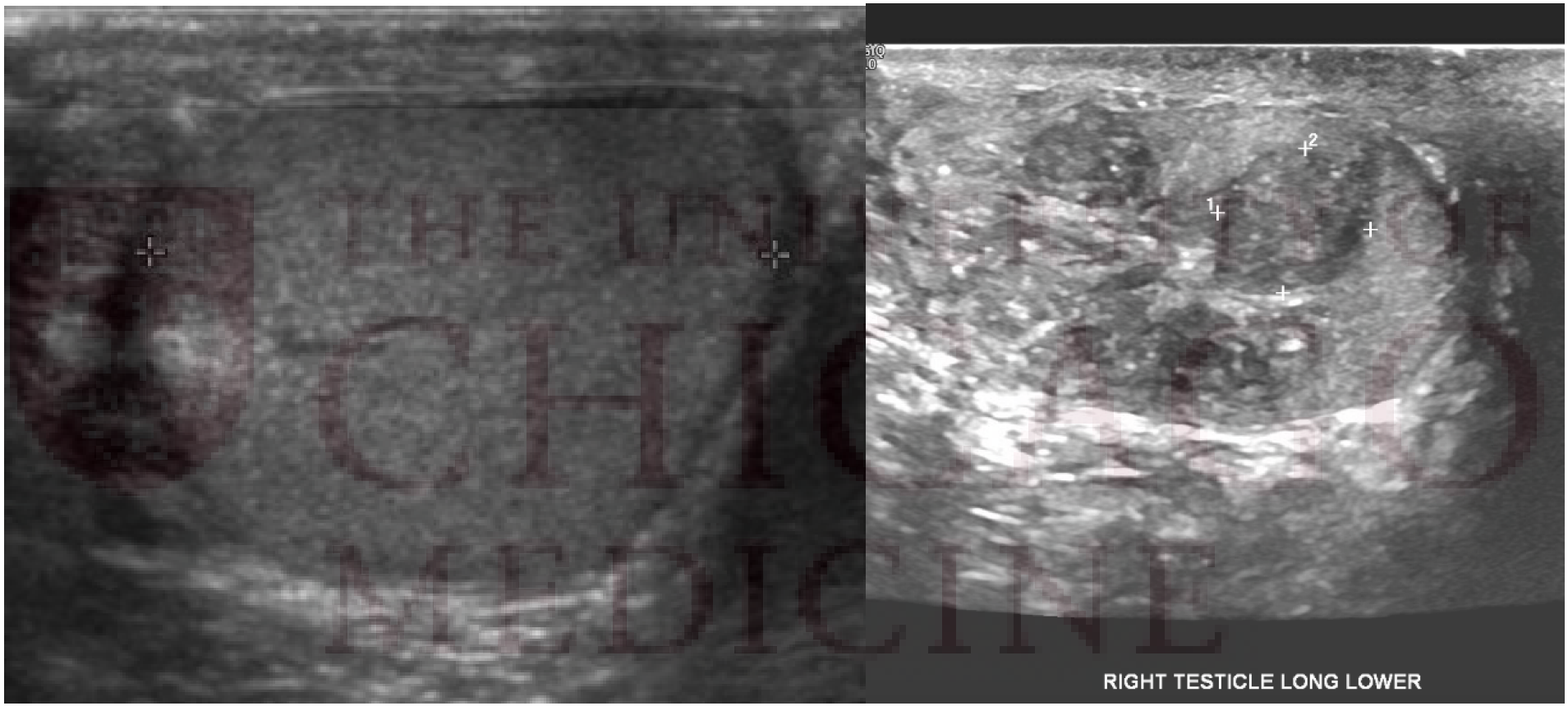
(Claahsen-van der Grinten, H, et al, 2022)

Lab and Treatment History

	11/2019	2/2020
17-HYDROXY PROGESTERONE (<220)	4,210	4,300
ALDOSTERONE (<21)		
RENIN (0.25-5.82)	4.6	3.6
Na		
K		
Total Testosterone (240 - 950 ng/dL)		
ACTH (<52 pg/mL)	299 (H)	166.5 (H)
Therapy adjustments after labs	Pred 7.5mg QHS Florinef 0.1mg BID	Pred 10mg Florinef 0.1mg BID

What about his testicular exam?

Testicular US



Testicular adrenal resting tumors (TARTs)

Pathophysiology

- Aberrant adrenal cells during embryology
- Have CYP11B1, CYP11B2 and ACTH and AII receptors
- Shown to have adrenal hormone synthesis
- Cause infertility by:
  - mechanical obstruction of the seminiferous tubules
  - Paracrine hormone secretion destroying Sertoli and germ cells

Screening

- Endo: Periodic screening after puberty
- US or MRI

Epidemiology

- 14% to 86% overall
- 25% in adolescents
- 46% in men

Risk factors

- Elevated ACTH
- Hormonal control has variable effect on incidence

Treatment

- ACTH suppression (dex)
- Surgery

What about his adult height?

He is currently 4’ 7”

Adult Height

JOURNAL ARTICLE

Adult Height in Patients with Congenital Adrenal Hyperplasia: A Systematic Review and Metaanalysis

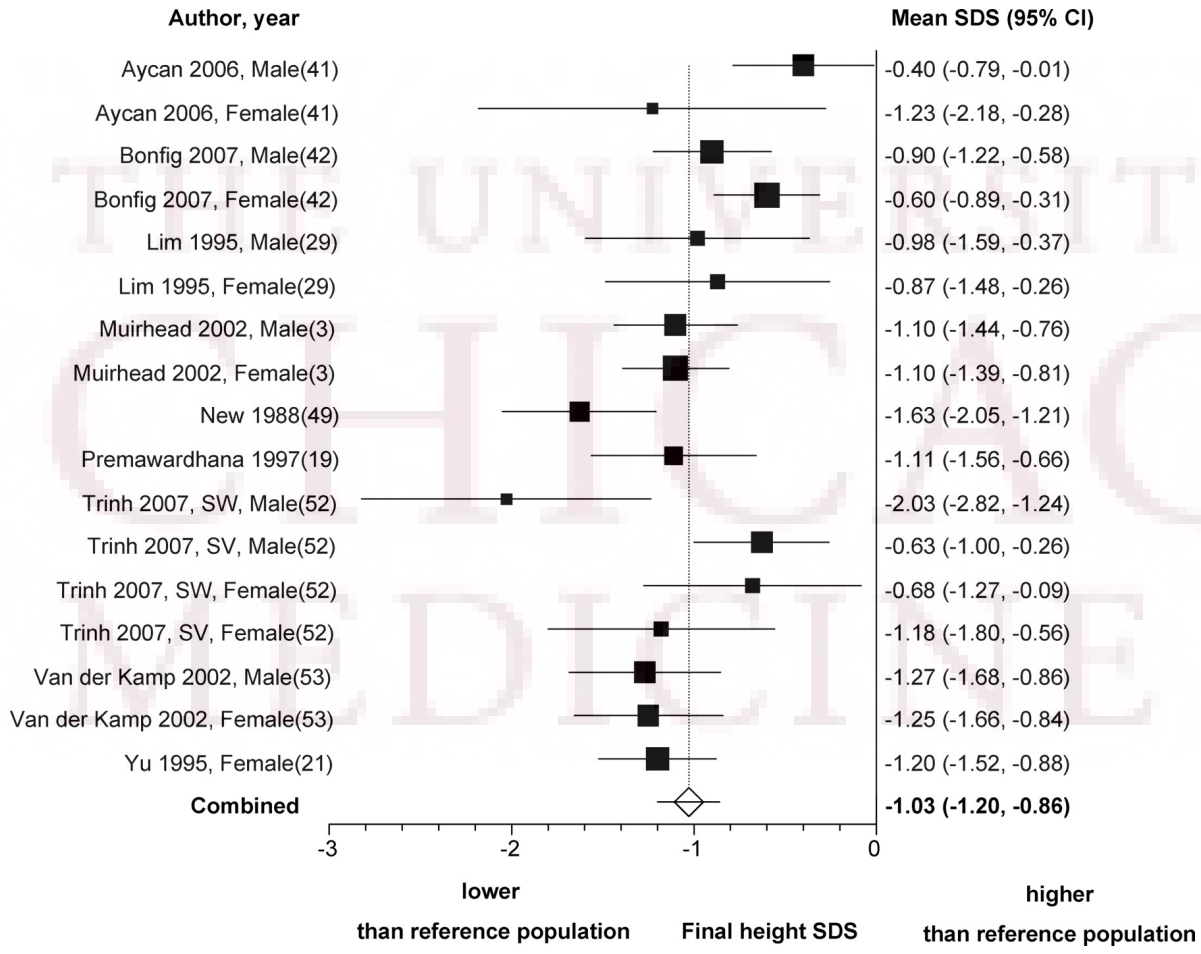
Kalpana Muthusamy, Mohamed B. Elamin, Galina Smushkin, Mohammad Hassan Murad, Julianna F. Lampropulos, Khalid B. Elamin, Nisrin O. Abu Elnour, Juan F. Gallegos-Orozco, Mitra M. Fatourechi, Neera Agrwal ... Show more

The Journal of Clinical Endocrinology & Metabolism, Volume 95, Issue 9, 1 September 2010, Pages 4161–4172, https://doi.org/10.1210/jc.2009-2616

Published: 01 September 2010 **Article history** ▾

Adult Height

Fig. 3. Random-effects metaanalysis of corrected-height SDS. ⋄, Overall estimate from the metaanalysis;



J Clin Endocrinol Metab, Volume 95, Issue 9, 1 September 2010, Pages 4161–4172, https://doi.org/10.1210/jc.2009-2616

What options do we have to increase adult height?

Leg Lengthening Procedures:

From Medical News Daily:

- Consider for leg length discrepancies
- Good posture
- Strengthen core muscles
- Use Ilizarov method
- Eat a nutritious diet
- One study of 131 patients
- Wear higher shoes…
  - Ages 16 – 67, mean of 25
  - Average length of 6.9 cm
  - Complications of 37%

Our patient underwent two leg lengthening procedures
4’7” → 4’9” → 4’11

(Novikov, K et al, 2014)

Returning to our patient

	10/6/22 8:08	9/27/23	12/29/23
17-HYDROXY PROGESTERONE (<220)	142	208	10300
ALDOSTERONE (<21)			<4
RENIN (0.25-5.82)	15	5.8	12
ACTH (<52 pg/mL)		66.7	884
Therapy adjustments after labs	Dex 0.25mg daily Florinef 0.1mg BID	HC 15mg and 5mg Florinef 0.1mg daily	

Attempting to enroll in Phase 3 clinical trial for:

Tildacerfont a CRF_1 receptor antagonist

Phase 2 results:

- ACTH: -59.4% to -28.4%
- 17-OHP: -38.3% to 0.3%

Product Candidate	Indication	Status	
Tildacerfont	Adult Classic Congenital Adrenal Hyperplasia	Topline results from CAHmelia-204 anticipated in the third quarter of 2024.	CAHMELIA STUDIES
	Pediatric Classic Congenital Adrenal Hyperplasia	Topline results from additional dose ranging in the fourth quarter of 2024.	CAHPTAIN STUDIES
	Polycystic Ovary Syndrome	Planned presentation of final data in an upcoming medical conference. Partnering opportunities available.	P.O.W.E.R. STUDY

Take Home Points

- Glucocorticoid therapy should be targeted for a mildly elevated 17-OH P and to decrease symptoms of glucocorticoid excess
- TARTs are extremely common and should be screened for in males.
- Surgical procedures exist for cosmetic height gain, although their use is cautionary

Thanks to Dr. Sarne!

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Lab and Treatment Full Table

	12/2015	4/2016	4/2017	10/2017	1/2019	7/2019	11/19	2/7/20 11:20	6/2/20 16:53	12/8/20 10:	10/6/22 8:08	9/27/23	12/29/23
17-HYDROXY PROGESTERONE (<220)	8346	271	245	83	10,317	6,030	4,210	4,300	8,290	129	142	208	10300
ALDOSTERONE (<21)	155				497	4.9							<4
RENIN (0.25-5.82)	20.93	13.28	22.23	16.5	13.53	7.6 (H)	4.6	3.6			15	5.8	12
Na K	135 4.6	140 4.2	139 4.0		140 3.7								
Total Testosterone (240 - 950 ng/dL)	115	463				606							
ACTH (<52 pg/mL)						224.8 (H)	299 (H)	166.5 (H)	200.4 (H)	< 1		66.7	884
Therapy adjustments after labs	HCT 25 BID, Florinef 0.05 BID	Dex 0.75mg Florinef 0.1mg daily	Dex 0.5mg Florinef 0.1mg daily	HCT 15mg and 5mg Florinef 0.1mg daily	HCT 20mg and 15mg Florinef 0.1mg daily	Pred 5mg QHS and 2.5mg Florinef 0.1mg BID	Pred 7.5 mg QHS Florinef 0.1 mg BID	Pred 10mg Florinef 0.1mg BID	Dex 0.5mg daily Florinef 0.1mg BID	Dex 0.5mg and 0.25mg alternating Florinef 0.1mg daily	Dex 0.25mg daily Florinef 0.1mg BID	HC 15mg and 5mg Florinef 0.1mg daily	