ENDO2019

E07. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline

ENDO2019

Guideline Writing Committee Members

Phyllis W. Speiser, MD (Chair)
Wiebke Arlt, MD, DSc
Richard J. Auchus, MD, PhD
Laurence S. Baskin, MD
Gerard S. Conway, MD
Deborah P. Merke, MD, MS
Heino F. L. Meyer-Bahlburg, PhD
Walter L. Miller, MD
M. Hassan Murad, MD
Sharon E. Oberfield, MD
Perrin C. White, MD

Plenary Panel Members

Moderator:

- Mitchell E. Geffner, MD

  Chief – Pediatric Endocrinology, Diabetes, and Metabolism; Professor of Pediatrics
  Children's Hospital Los Angeles; Keck School of Medicine of USC, CA

Panel:

- Phyllis W. Speiser, MD (Chair)

  Chief – Pediatric Endocrinology, Cohen Children's Medical Ctr of New York
  Professor of Pediatrics, Zucker School of Medicine at Hofstra/Northwell, NY

- Walter L. Miller, MD

  Distinguished Professor Pediatrics, Emeritus, University of California, San Francisco, CA

- Deborah P. Merke, MD, MS

  Senior Investigator, National Institutes of Health, MD

- Richard J. Auchus, MD, PhD

  Professor, University of Michigan, MI

ENDO2019

Disclosures

Mitchell E. Geffner, MD – Consultant: Spruce Biosciences, BridgeBio Pharma, Millendo, Novo Nordisk, Tolmar, Nutrition & Growth Solutions, Sandoz; Speaker: Pfizer, Inc.

Phyllis W. Speiser, MD – Consultant: Gerson Lehman Group, Neurocrine Biosciences

Richard J. Auchus, MD, PhD – Consultant: Novartis Pharmaceuticals, Jansen Pharmaceuticals, Quest Diagnostics, Corcept Therapeutics, Adrenas Therapeutics, Neurocrine Biosciences, Spruce Biosciences, Strongbridge Biopharma, Selenity Therapeutics; Grant Recipient: Novartis Pharmaceuticals, Neurocrine Biosciences, Spruce Biosciences, Strongbridge Biopharma

Deborah P. Merke, MD, MS – Research Investigator: Diurnal, Spruce Biosciences

Walter L. Miller, MD – Consultant: Spruce Biosciences, Adrenas Therapeutics

Plenary Format

1. Overview of Congenital Adrenal Hyperplasia Guideline (Dr. Speiser)
2. Cases (Dr. Miller, Dr. Merke, Dr. Auchus):
   a. Multiple choice question with audience response
   b. Panel discussion of case
   c. Relevant guideline recommendations
   d. Q&A related to case
      - *Audience may submit questions at any time during case*

Access Guideline and Other Resources

Guideline

J Clin Endcrinol Metab 2018; 103(11): 4043-4088

Guideline Resource Page

https://www.endocrine.org/CPGcah

- Full published guideline
- Guidelines Pocket Card
- Online patient resources
- Interview with the Guideline Writing Committee Chair

Overview of Guideline

Phyllis W. Speiser, MD

Chief, Pediatric Endocrinology,

Cohen Children's Medical Ctr of NY

Professor of Pediatrics,

Zucker School of Medicine at Hofstra/Northwell

ENDO2019

Learning Objectives

1. To improve understanding of the rationale behind treatment of CAH due to steroid 21-hydroxylase deficiency

2. To update what is known about the pediatric and young adult health outcomes of CAH due to steroid 21-hydroxylase deficiency and how to optimize treatment

Newborn Screening

- Trend toward gestational age (and/or birthweight) stratification of newborn screening cut-points
- Demonstrated utility of a second screen at ~2 weeks of life to enhance PPV
- Increased utilization of tandem mass spectrometry as a second tier test

Prenatal Diagnosis & Treatment

- Proof of concept: Fetal cell-free DNA *CYP21A2* genotype

- Prenatal dexamethasone: Not recommended
  - Increasing animal and human data implicating irreversible SAEs in offspring of treated pregnancies

Medical Management

- Growing children:
  - Limit glucocorticoid dose to maintain adrenal precursors in high-normal range
  - Teach sick day and emergency management
  - Avoid treatment for NCCAH unless symptomatic
- Women of child-bearing age:
  - Maintain serum progesterone = <0.6 ng/mL (<2 nmol/L)
  - Consider glucocorticoid treatment in NCCAH females with sub-fecundity
- Men:
  - Maintain androstenedione : testosterone ratio = <2 (normal = <0.5)

Steroid Measurements

- 21-deoxycortisol useful in diagnosis and monitoring treatment
- 11-ketotestosterone and related metabolites aid understanding of androgen excess conditions

Cardio & Metabolic Outcomes

- Meta-analysis showed slightly higher systolic and diastolic BP in children and adults with CAH, BUT *no direct evidence of increased CV morbidity and mortality*

- No evidence for type 2 diabetes
  - Gestational diabetes 2X increased in CAH females

Tamhane SU, et al. JCEM 2018

Interpreting High 17OHP Values on Newborn Screening for Congenital Adrenal Hyperplasia (21-Hydroxylase Deficiency)

Walter L. Miller, MD

Distinguished Professor Pediatrics, Emeritus

University of California San Francisco

ENDO2019

Case 1 – Newborn Boy

- 3600-gram term newborn boy
- Family lacks insurance, has experienced caregivers at home, and demands early discharge
- Newborn screen sent at discharge at 18 hours
- Serum 17OHP comes back 3100 ng/dL (~90 nmol/L), above upper limit of normal of 2240 ng/dL (~70 nmol/L)

Case 1 – Newborn Boy

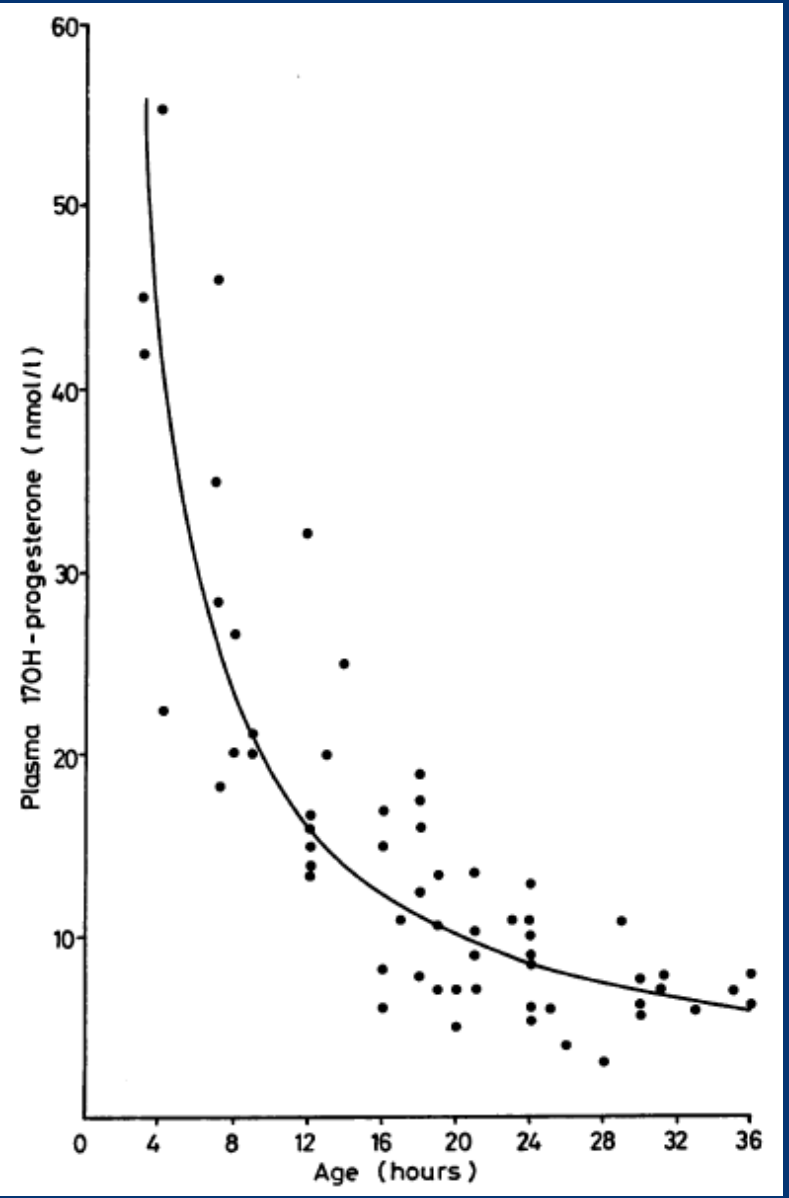
Is this a true positive?

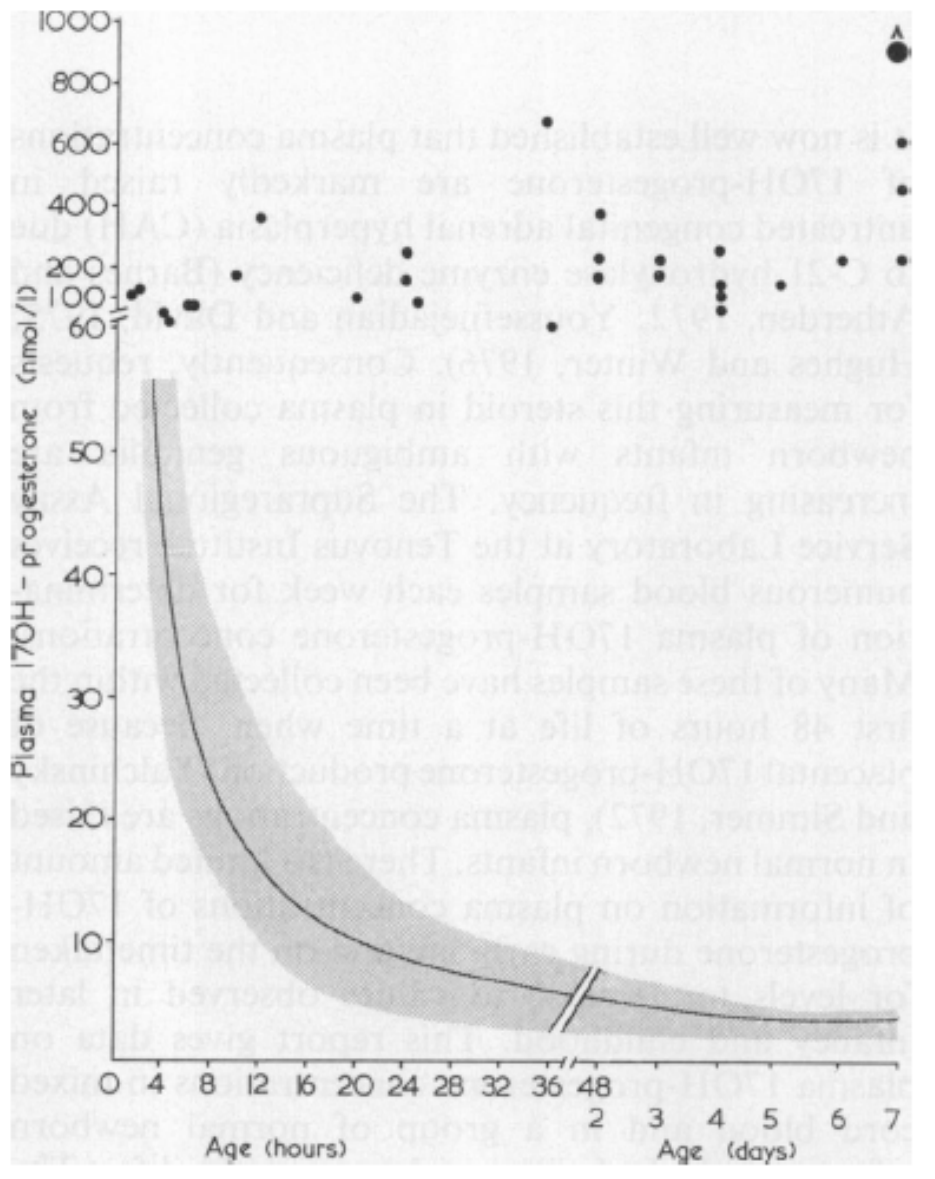
A. Yes
B. No

What do you do?

A. Repeat the serum 17OHP
B. Perform a cosyntropin stimulation test
C. Wait for the results of the newborn screening test
D. Start treatment with glucocorticoid plus mineralocorticoid

Newborn 17OHP Values (Hughes, 1979)





Case 2 – Newborn Phenotypic Female

- 3.4-kg normal newborn phenotypic female discharged from newborn nursery after newborn screen obtained at 39 hours of age

- Day 8: Screen 17OHP = 6140 ng/dL (~200 nmol/L). Seen at local ER: looks fine and vital signs stable; Na = 135, K = 5.3, and HCO_3 = 21

- Day 13: Back to ER. Clinically dehydrated. Wt = 3.0 kg; Na =126, K = 7.9, HCO_3 = 19, and BUN = 21. Karyotype sent. Repeat 17OHP = 8230 ng/dL (249 nmol/L; nl <200 ng/dl or <6 nmol/L).
  - Rx'ed with fluids and hydrocortisone
  - PE: Increased pigmentation of areolae and labiae, no clitoromegaly, and no posterior fusion
  - Admitted to PICU

Case 2 – Newborn Phenotypic Female*(continued)*

- FH: Sister with salt loss; male cousin with DSD & SW
- PRA = 2738 ng/dL/hr (649 pmol/L/hr, nl 200-3500 ng/dL/hr = 47-829.5 pmol/L/hr)
- Androstenedione = 2408 ng/dL (84 nmol/L, nl <52 ng/dL = <1.8 nmol/L)
- 17OHP = 10,800 ng/dL (327 nmol/L, nl <200 ng/dL = <6 nmol/L)
- Progesterone = 1240 ng/dL (39.4 nmol/L, nl <10 ng/dL = <0.3 nmol/L)
- Provisional Dx: Salt-wasting 21OHD
- Rx: 'High-dose' hydrocortisone, fludrocortisone, and NaCl
- HC reduced to 5 mg/m^2/day for 5 days; then held for 36 hours
- All STEROIDS UNMEASURABLE before and after ACTH, except DHEA = 16 ng/dL (0.56 nmol/L, basal) and 73 ng/dL (2.5 nmol/L, post-ACTH)
- Karyotype = 46,XX

Case 2- Newborn Phenotypic Female

What is your diagnosis?

A. 21-Hydroxylase deficiency
B. 11β-Hydroxylase deficiency
C. P450-Oxidoreductase deficiency
D. 3β-Hydroxysteroid dehydrogenase deficiency

dDx (or ∂Dx) of an ↑17OHP on the Newborn Screen

1. “Normal” premature infant
2. Sick preemie
3. Sick term baby
4. 21-Hydroxylase deficiency
5. 11-Hydroxylase deficiency
6. 3β-Hydroxysteroid dehydrogenase deficiency
7. P450 Oxidoreductase deficiency
8. (17,20-Lyase deficiency from b5 deficiency)
9. (AKR1C2/4 deficiency)

ENDO2019

Moderator Questions for the Panel & Discussion

Guideline Recommendations Relevant to Answer to Case Questions

- Newborn screening ONLY tests for CAH due to 21-hydroxylase deficiency.

- Confirmation of the correct diagnosis should be done by performing a cosyntropin (ACTH 1-24) stimulation test and measuring the full profile of adrenocortical steroid levels.

Audience Questions on Newborn Screening?

Diagnosis and Treatment During Childhood

Deborah P. Merke, MD, MS
Senior Investigator,
National Institutes of Health

Case 1: School-age child

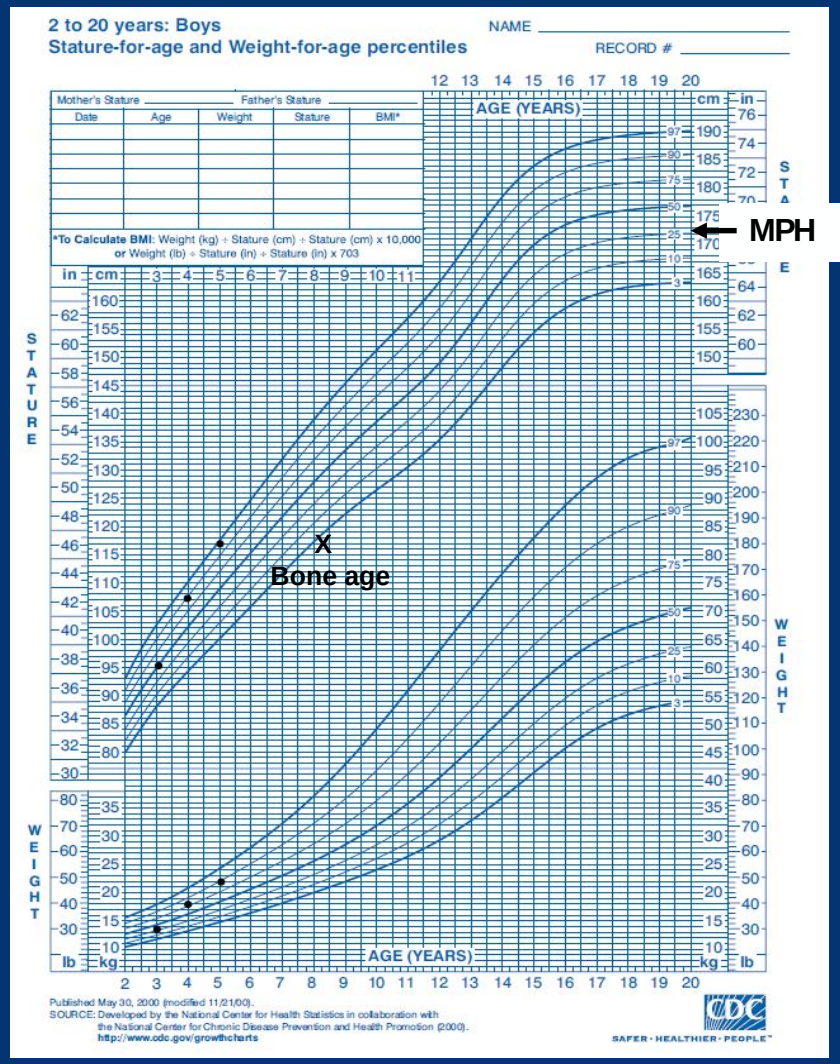
5-year-old boy presents with body odor, pubic hair, and increased growth velocity

PE: BP 86/54 mm Hg, Tanner 3 pubic hair, and testes 2 cc

Bone age = 8 years

17OHP = 753 ng/dL (22.8 nmol/L)

Testosterone = 50 ng/dL (1.7 nmol/L)



ENDO2019

Cosyntropin Stimulation Test

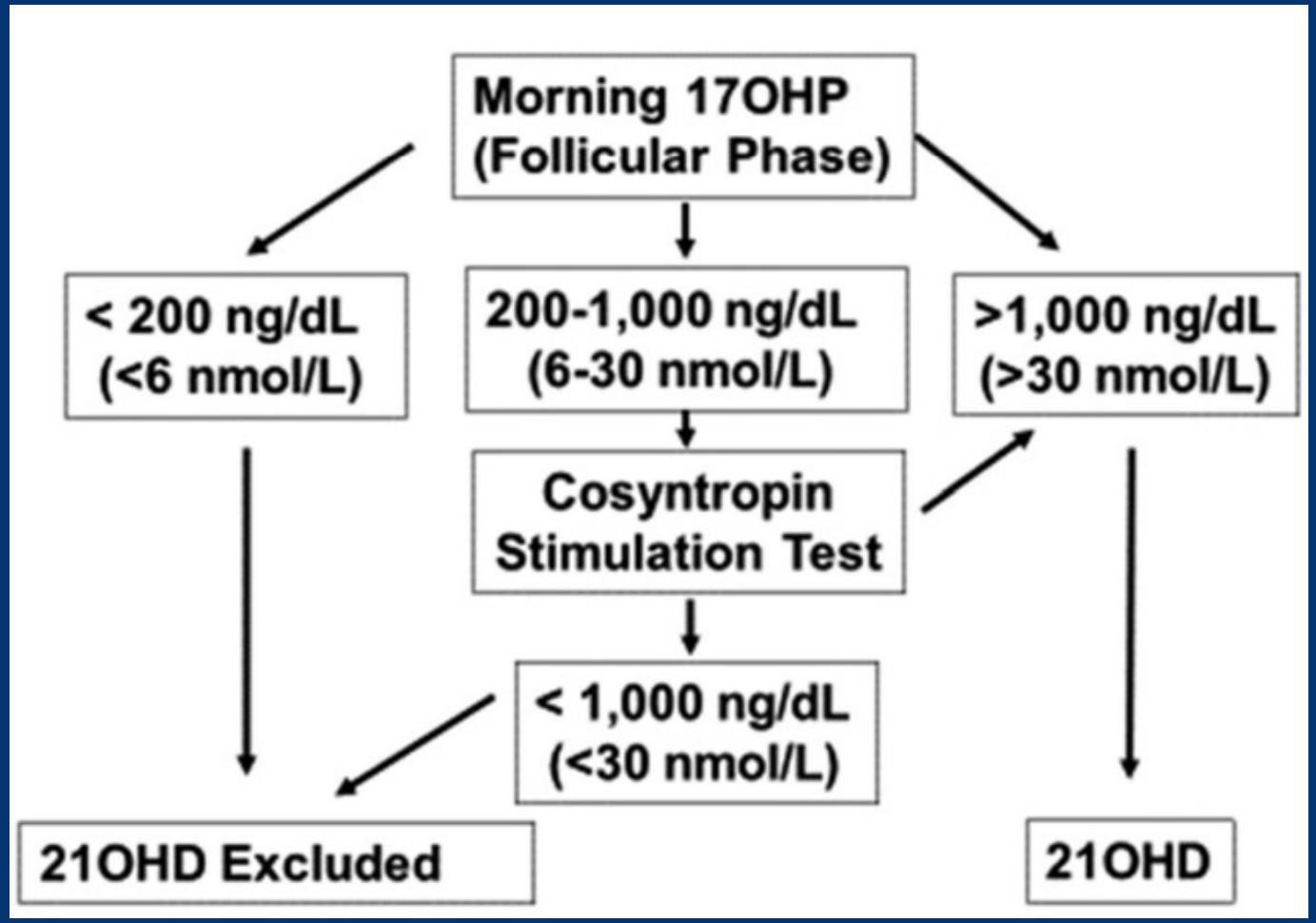
	Baseline	60 minutes
17-OHP	1067 ng/dL (32.3 nmol/L)	6790 ng/dL (205 nmol/L)
Cortisol	6.8 μg/dL (187 nmol/L)	16.2 μg/dL (447 nmol/L)

Cosyntropin Stimulation Test

Q1: Which of the following would you recommend?

A. Follow clinically; this patient has non-classic CAH
B. Treat with hydrocortisone; this patient has non-classic CAH
C. Treat with hydrocortisone and fludrocortisone; this patient has classic simple-virilizing CAH
D. Genotype to determine diagnosis

Diagnosis: Childhood and Adulthood



- Classic CAH: unstimulated 17OHP several thousand
- Non-classic CAH: randomly measured 17OHP can be normal
- Genotyping if hormonal evaluation equivocal

Q2: What is the “best” long-term plan for transition from adolescence to adulthood?

A. Continue hydrocortisone; non-classic patients are easily managed on short-acting glucocorticoid
B. Switch to a longer-acting glucocorticoid medication to optimize compliance
C. Discontinue hydrocortisone during puberty; non-classic males do not require lifelong glucocorticoid therapy

Case 2: Child with Illness

A 3-year-old female with classic CAH awakens with watery diarrhea and vomits once. Her temperature is 38˚C. She is now tolerating fluids at 10 AM.

Her usual medications are: hydrocortisone 2.5 mg thrice daily (9.4 mg/m^2/day) and fludrocortisone 100 mcg daily.

Case #2 Child with Illness

You should instruct her parents to:

A. Encourage frequent fluid intake with ingestion of simple and complex carbohydrates and no change in medication
B. Administer intramuscular hydrocortisone 25 mg and take to ER for immediate evaluation
C. Stress dose orally every 6 hours with double her daily HC dose and encourage frequent fluid intake with ingestion of simple and complex carbohydrates
D. Double her fludrocortisone dose and encourage frequent fluid intake

Case 2: Child Undergoing Anesthesia

A few months later, this child is scheduled for cystoscopy under anesthesia.

What do you recommend for glucocorticoid dosing?

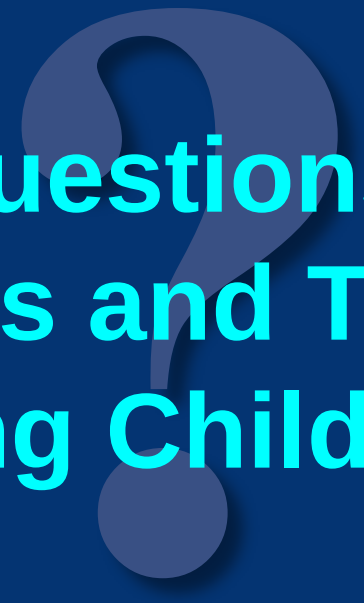
A. No change in her usual medications
B. Administer intramuscular/intravenous hydrocortisone 25 mg prior to the procedure and resume usual hydrocortisone doses following the procedure
C. Administer intramuscular/intravenous hydrocortisone 50 mg prior to the procedure and double oral hydrocortisone doses for 24 hours following the procedure
D. Double oral hydrocortisone dose for one day prior and on the day of the procedure

Moderator Questions for the Panel & Discussion

Guideline Recommendations Relevant to Answer to Case Questions

- Treat nonclassic CAH patients who are symptomatic
  - Children with rapidly advancing pubarche
  - Adolescents or adults with symptoms of androgen excess or fertility issues
- Avoid treating males with nonclassic CAH who have completed growth and puberty
- Use glucocorticoid stress-dosing judiciously for major surgical procedures and febrile or gastrointestinal illness

Audience Questions Regarding Diagnosis and Treatment During Childhood



CAH in the Young Adult

Richard J. Auchus, MD, PhD
University of Michigan
Ann Arbor VA Medical Center

ENDO2019

A Young Woman

- 22-year-old woman with classic (“simple-virilizing”) 21-hydroxylase deficiency diagnosed at birth in transition from pediatrics
- Rx hydrocortisone 10 mg 3 times daily with meals + fludrocortisone 0.1 mg QHS
- Regular menses, not sexually active, and not planning pregnancy
- Doubles hydrocortisone for illness ~Q6 months
- Last hydrocortisone injection 7 years ago; no recent crises
- Some fatigue during the day not improved with hydrocortisone
- Sleeps well; does not shave or pluck

A Young Woman

- **Exam**
  - **No acne or coarse facial hair**
  - **No purple striae, muscle weakness, or skin thinning**
  - **BMI 27.5 kg/m^2**
  - **Sitting BP 105/65 mm Hg and HR 85/min**
- **She took hydrocortisone today at 6 AM, and her blood is drawn at 11 AM**

A Young Woman

Laboratory test results:

- Sodium = 138 mEq/L
- Potassium = 4.7 mEq/L
- Plasma renin mass = 85 pg/mL (4-44 pg/mL)
- Serum DHEA-S = <15 µg/dL (44-332 µg/dL) (SI: <0.41 µmol/L [1.19-9.00 µmol/L])
- Serum testosterone = 40 ng/dL (8-60 ng/dL) (SI: 1.4 nmol/L [0.3-2.1 nmol/L])
- Serum androstenedione = 180 ng/dL (80-240 ng/dL) (SI: 6.2 nmol/L [2.79-8.38 nmol/L])
- Serum 17-hydroxyprogesterone = 4500 ng/dL (<80 ng/dL [follicular]) (SI: 136.4 nmol/L [<2.42 nmol/L])

Which of the following changes to her management would you recommend?

A. No changes
B. Increase the morning dose of hydrocortisone to 15 mg
C. Switch hydrocortisone to dexamethasone 1 mg at bedtime
D. Increase the fludrocortisone dosage to 0.2 mg daily
E. Reduce the fludrocortisone dosage to 0.05 mg daily

Maintenance Therapy Suggested in Fully Grown Patients

Table 3. Maintenance Therapy Suggested in Fully Grown Patients

Type of Long-Acting Corticosteroid	Suggested Dose (mg/d)	Daily Doses
HC	15–25	2–3
Prednisone	5–7.5	2
Prednisolone[a]	4–6	2
Methylprednisolone	4–6	2
Dex[a]	0.25–0.5	1
Fludrocortisone	0.05–0.2	1–2

[a]Suspension or elixir may permit improved dose titration for these drugs.

ENDO2019

A Young Woman

- Fatigue improves with fludrocortisone increase to 0.2 mg /day
- Remains on stable regimen for 4 years
- Recently married and plans to conceive
- Having unprotected intercourse twice weekly for 4 months
- Has regular monthly menses, but has not conceived

Laboratory test results (10 AM blood draw):

- Plasma renin mass = 25 pg/mL (4-44 pg/mL)
- Serum testosterone = 40 ng/dL (8-60 ng/dL)

  (SI: 1.4 nmol/L [0.3-2.1 nmol/L])
- Serum androstenedione = 90 ng/dL (80-240 ng/dL)

  (SI: 3.14 nmol/L [2.79-8.38 nmol/L])

Which additional laboratory test should you order?

A. Morning pre-hydrocortisone serum testosterone
B. Plasma ACTH
C. Follicular-phase serum progesterone
D. Serum 17-hydroxyprogesterone
E. Serum estradiol

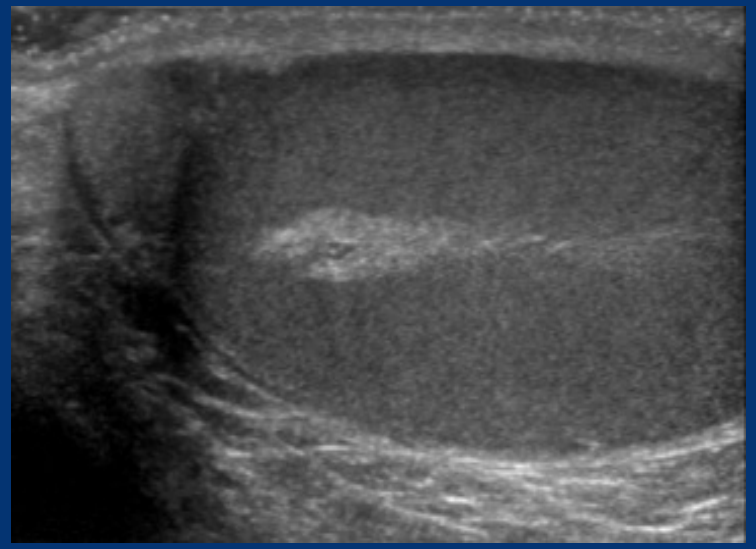
A Young Man

If the patient were a man of the same age with classic 21-hydroxylase deficiency, what factors should be considered as contributing to infertility?

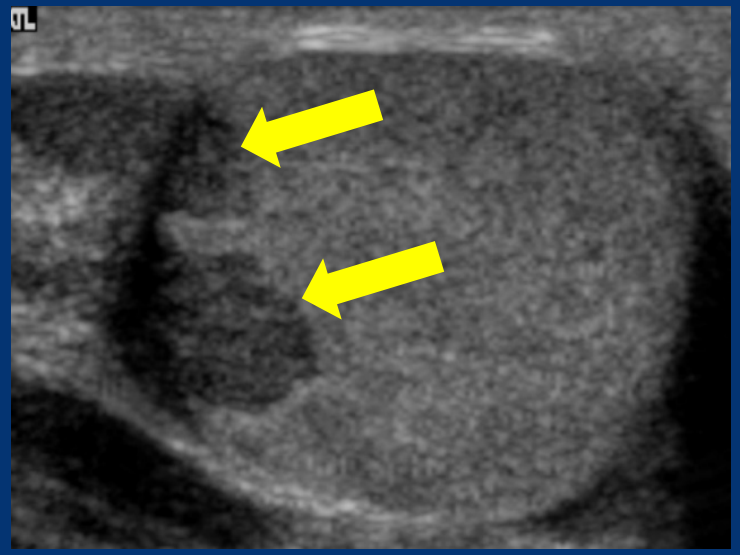
A. Adrenal-derived androgens
B. Testicular adrenal rest tumors
C. Gonadotropin suppression
D. Testicular failure
E. All of the above

Testicular Adrenal Rest Tumors (TARTs)

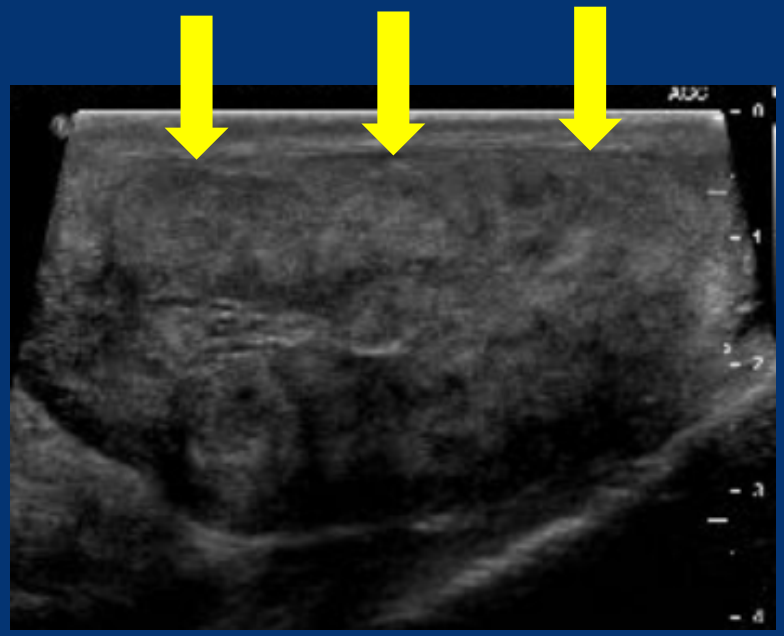
- Tumors <2 cm typically not palpable
- Ultrasound = modality of choice for detection and monitoring



Normal testis



Small TART surrounding the mediastinum testes



Advanced TART

ENDO2019

Laboratory Monitoring of CAH in Adults

Table 5. Utility of Various Analytes for Monitoring CAH Treatment

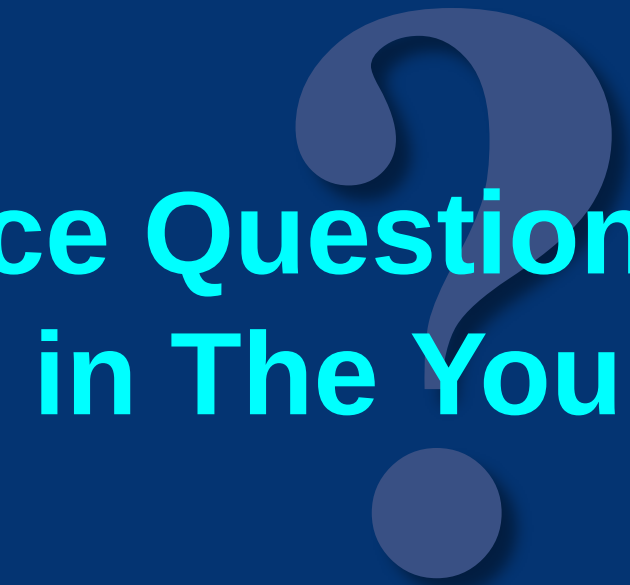
Patients	Analyte	Physiology	Goals and Comments
All ages	Plasma renin	Volume status	Low to normal unless hypertensive
	Potassium	MC replacement	Goal is normal
	Sodium	GC and MC replacement	Goal is normal
	Testosterone	Total androgens	Goal is at or near normal
	Androstenedione	Mostly adrenal origin	Goal 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

Moderator Questions for the Panel & Discussion

Guideline Recommendations Relevant to Answer to Case Questions

- In adults with classic congenital adrenal hyperplasia:
  - Use daily hydrocortisone and/or long-acting glucocorticoids plus mineralocorticoids, as clinically indicated
  - Monitor for signs of glucocorticoid excess, inadequate androgen normalization, and mineralocorticoid deficiency or excess
  - Annual exam: blood pressure, body mass index, and Cushingoid features
  - Biochemical measurements to assess glucocorticoid and mineralocorticoid replacement using consistently timed hormone measurements
  - Do not completely suppress endogenous adrenal steroid secretion
- In males, periodic testicular ultrasound to assess for the development of testicular adrenal rest tumors (TARTs)

Audience Questions Regarding CAH in The Young Adult?



SUMMARY

- Although steroid 21-hydroxylase deficiency (21OHD) is most common, obtain a full adrenal steroid profile before and after cosyntropin to exclude other forms of CAH
- LC-MS/MS is the assay of choice for steroid measurements
- Treat classic CAH 21OHD with both glucocorticoid AND mineralocorticoid, and monitor 17OHP, androstenedione (A), and renin
  - Update stress-dosing education frequently
- Not all individuals with nonclassic CAH require glucocorticoid treatment
- If pregnancy is desired, maintain serum progesterone = <0.6 ng/mL (<2 nmol/L) in females and A:T ratio = <2 in males

ENDO2019