Case: A lean 22 y/o woman is hirsute and has oligomenorrhea. She presents because of infertility (the absence of pregnancy after 1 year of regular, unprotected sex). What is in the differential diagnosis of infertility in a hirsute woman?

Learning objectives

At the conclusion of this presentation, the laboratorian will be able to:

- List a differential diagnosis of hirsutism and infertility
- Classify and differentiate the different varieties of CAH
- Diagnose and treat late-onset CAH

Differential diagnosis of infertility in a hirsute woman:

- Polycystic ovarian syndrome (PCOS; associated w/ MS)
- Medications (e.g., danazol for endometriosis)
- Late-onset congenital adrenal hyperplasia
- Cushing syndrome
- Androgen secreting tumors (ovarian or adrenal)
- Precocious adrenarche (early-onset axillary and/or pubic hair)
What is congenital adrenal hyperplasia (CAH)?

(I) Inborn error in steroid biosynthesis: variable impairment in the synthesis of:

- Cortisol (alone)
- (or)
- Cortisol & Aldosterone

(II) Disordered adrenal androgen production

- Shared biosynthetic pathways w/ testes & ovary

- Adrenal androgens: precursors of estrogens
- precursors of androgens

What are the consequences of disordered adrenal androgen synthesis in congenital adrenal hyperplasia (CAH)?

<table>
<thead>
<tr>
<th>Excess</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>In utero</td>
<td>Genital hyperpigmentation</td>
<td>Virilation → 46,XX DSD</td>
</tr>
<tr>
<td>Ex utero</td>
<td>Precocious puberty</td>
<td>Accelerated growth (children); virilation</td>
</tr>
</tbody>
</table>

Testosterone deficiency

<table>
<thead>
<tr>
<th>In utero</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate virilation</td>
<td>No adverse effect</td>
<td></td>
</tr>
<tr>
<td>46,XY DSD</td>
<td>No adverse effect</td>
<td></td>
</tr>
<tr>
<td>Ex utero</td>
<td>46,XY DSD</td>
<td>No adverse effect</td>
</tr>
</tbody>
</table>

What is the most common form of congenital adrenal hyperplasia (CAH)?

Def. of 21-alpha hydroxylase (21-OHylase)

- Formal gene name: CYP21A2*

*Cytochrome P450, Family 21, Subfamily A, Polypeptide 2:
CYP21A2P = Cytochrome P450, Family 21, Subfamily A, Polypeptide 1 Pseudogene

CYP21A2

CYP21A2

CYP21A2
What regulates the expression of 21-OHylase?

CRH → [↑] → CRH
Hypothalamus
Anterior pituitary (corticotrophs)

ACTH
Adrenal cortex (fasciculata, reticularis)

Cortisol

Enzymes regulated by ACTH

- STAR
- 20,22 desmolase* (CYP11A1)
- 17-OHylase (CYP17)
- 3-beta HSD
- 21-OHylase (CYP21A2)
- 11-beta hydroxylase (CYP11B1)

STAR = steroid acute regulatory protein; transports chole into adrenal cortical cells; * a.k.a. − side-chain cleavage enzymes.
(1) Excellent data for their regulation by ACTH.

What are the consequences of adrenal steroid hormone deficiency?

<table>
<thead>
<tr>
<th>Hormone def.</th>
<th>Consequences:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>Lack energy, N/V, weight loss, hypoglycemia, hyponatremia, vascular collapse, hypotension, shock, death</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Hyponatremia, hyperkalemia, acidosis, hypovolemia, hypotension, shock, death</td>
</tr>
</tbody>
</table>

What is the biochemistry of 21-OHylase def.?
What are other forms of CAH?

Other types of CAH:

- 11-beta hydroxylase def.
- 17-alpha hydroxylase def.
- 3-beta hydroxy steroid dehydrogenase def. (3-beta HSD def.)
- Lipoid CAH [steroidogenic acute regulatory (StAR) protein def.]

What is the range of consequences of 21-OHylase def.?

<table>
<thead>
<tr>
<th>Severity</th>
<th>Classification</th>
<th>Phenotype of 21-OHylase CAH</th>
<th>Age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>++++</td>
<td>Classical</td>
<td>Salt-wasting</td>
<td>Newborns</td>
</tr>
<tr>
<td>+++</td>
<td>Classical</td>
<td>Simple virilizing</td>
<td>Newborns</td>
</tr>
<tr>
<td>++</td>
<td>Nonclassical*</td>
<td>Late-onset</td>
<td>Late childhood, adolescence or adulthood</td>
</tr>
<tr>
<td>+</td>
<td>Heterozygous</td>
<td>Asymptomatic carrier</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Attenuated; N/A = not applicable
What is effect of *salt-wasting* or *simple virilizing* CAH on the development of the external genitalia in the 46,XX fetus?

Excess adrenal androgens (androstenedione & DHEA)
- Virilization of external genital
- Disorder of sexual development (DSD) [46,XX, DSD]

How do salt-wasting and simple virilizing CAH differ?

<table>
<thead>
<tr>
<th></th>
<th>Salt-wasting</th>
<th>Simple virilizing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol def.</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Aldosterone def.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Addisonian crisis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Addisonian crisis (if untx'ed)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
What is the epidemiology of late-onset of 21-OHylase def.?

Hz: 1 in 1000

Incr. Hz in: Ashkenazi Jewish, Mediterranean, Middle-Eastern and Indian populations

Note: Dx may be missed in boys

What is the phenotype of late-onset of 21-OHylase def. in females?

Androgen excess:
- Hirsutism (59%), acne (33%), androgenic alopecia, anovulation, menstrual dysfunction (54%: oligomenorrhea) & infertility

Prepubertal:
- +/- Tall stature, advanced skeletal maturation, and premature development of pubic hair, axillary hair, and adult apocrine odor;
- +/- Clitoromegaly

Women: Polycystic ovary-like phenotype

Note: Boys may have penile enlargement with prepubertal growth.

How is the diagnosis of late-onset CAH established?

Compatible clinical history of androgen excess:
- Girls: +/- premature adrenarche, accelerated growth
- Girls, adolescents/women: acne, hirsutism
- Adolescents/women: menstrual dysfunction & infertility

Elevated basal and 60 min. post-ACTH 17-OHP

**Normal range**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (T)</td>
<td>5-15</td>
</tr>
<tr>
<td>Androstenedione (A)</td>
<td>10-50</td>
</tr>
<tr>
<td>Dehydroepiandrosterone sulfate (DHA-S)</td>
<td>100-600</td>
</tr>
<tr>
<td>3α-diol</td>
<td>10-50</td>
</tr>
<tr>
<td>5α-reductase</td>
<td>&gt; 50</td>
</tr>
</tbody>
</table>

Other hormone measurements in late-onset CAH

- T = Testosterone
- A = Androstenedione
- DHA-S = Dehydroepiandrosterone sulfate
- 3α-Diol = Urinary 3α-androstenediol glucuronide
- 5α-reductase = Activity of T → DHT converting enzyme

* Marker of peripheral androgen metabolism

**What are complications of late-onset of 21-OHylase def.?**

- Adrenal tumors
- Adrenal hypertrophy
- Adrenal myolipoma (rare)
What is in the *differential diagnosis* of late-onset of 21-OHylase def.?

- Conditions producing hirsutism and/or menstrual irregularities (including infertility)
- Polycystic ovarian syndrome (PCOS)
- Medications (e.g., danazol for endometriosis)
- Cushing syndrome
- Androgen secreting tumors (ovarian or adrenal)
- Precocious adrenarchy (early-onset axillary and/or pubic hair)

How can hirsutism be evaluated (not exhaustive)?

<table>
<thead>
<tr>
<th>Menses</th>
<th>Close (regular)</th>
<th>Suddenly irregular, severe and/or rapid</th>
<th>Chronically irregular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tumor

HAIR-AN (type A ins.res., IR or post-IR mutations)

PCOS (metabolic syndrome)

Obese

Non-obese

Late-onset CAH

HAIR-AN syndrome is defined as a constellation of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN).

How is late-onset of 21-OHylase def. excluded from the differential diagnosis of hirsutism or menstrual irregularity (including infertility)?

17-OHP
- Basal & Post-ACTH

<table>
<thead>
<tr>
<th>17-OHP</th>
<th>Normal</th>
<th>Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-onset CAH</td>
<td>Ruled out</td>
<td>Late-onset CAH</td>
</tr>
</tbody>
</table>
How and when should late-onset of 21-OHylase def. be treated? (1)

<table>
<thead>
<tr>
<th>Girls &amp; boys</th>
<th>Treatment</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>W/ pre-, early puberty (+) incr. BA</td>
<td>Glucocorticoids (+/- GnRH agonist for precocious puberty)</td>
<td>Decr. rate of skeletal maturation incr. final height</td>
</tr>
</tbody>
</table>

Pubertal girls

| ACTH-stimulated Cortisol: <18 mcg/dL | Glucocorticoids | Tx glucocorticoid def.; prevent Addisonian crisis |
| => 18 mcg/dL | Glucocorticoids | Tx at times of stress; prevent Add.crisis |

BA = bone age

How should late-onset of 21-OHylase def. be treated in adult women? (2)

<table>
<thead>
<tr>
<th>Oral contraceptives</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/- decr. ovarian androgen secretion, improve acne, slow hirsutism, restore menstrual cyclicity</td>
<td></td>
</tr>
</tbody>
</table>

| Antiandrogens* | +/- helpful for hirsutism androgenic alopecia |
|* spironolactone, flutamide, cyproterone acetate, or finasteride

SUMMARY

Classical 21-OHylase CAH

Fetus -- > virilization: 46, XX DSD

Newborn: +/- Addisonian crisis
- salt-losing versus simple virilizing

Late-onset CAH (nonclassical CAH): common disorder

 Presents as hirsutism, menstrual irregularity, infertility

Men: asymptomatic

Tx. w/ glucocorticoids if low cortisol response to ACTH
THE END