Males with CAH – specific focus on fertility

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Todd D. Nebesio, M.D., FAAP
Associate Professor of Clinical Pediatrics
Reproductive problems in CAH

- Increased risk of reduced fertility and reproductive problems in women and men

- **Females**
  - #1 reason is suboptimal control of CAH
  - Often reversible but depends on exact reason

- **Males**
  - #1 reason is testicular adrenal rest tumors
  - Potentially reversible if detected early
TARTs in males with CAH

- Testicular adrenal rest tumors = TARTs

- First reported in 1940
  - Morphologically and functionally resemble adrenal gland tissue

- Not malignant but they can cause testicular damage and lead to fertility problems
TARTs resemble adrenal tissue

- Adrenal glands develop close to the testicles
  - Some cells destined to become adrenal gland cells may nestle within part of the testicles
  - Up to 15% of healthy newborn males can have adrenal rest cells

- ↑ ACTH levels cause adrenal rest cells to grow
  - Most commonly seen in males with poor CAH control
  - TARTs can also occur in adequately controlled males and they do not always occur in those with poor biochemical control
Hypothalamic-Pituitary-Adrenal Axis

- Hypothalamus
- Corticotropin releasing hormone (CRH)
- Pituitary
- Adrenocorticotropin hormone (ACTH)
- Adrenal glands
- Cortisol
- Androgens
TARTs in CAH

- **Prevalence:** 0% to 94% – increases with age
  - Most commonly seen in adolescent and adults with salt-wasting CAH

- **Bilateral in more than 80% of cases**
  - Usually cannot feel (unless > 2 cm)

- **Discovered in < 8 week olds at autopsy**

- **Ultrasound studies**
  - 21% to 24% of pre-pubertal males
  - Detected as young as 6 to 7 years old
TARTs and reduced fertility

• Majority of adolescent and adult males with CAH have one or more tumors
  – Most are only detected by ultrasound or MRI

• In adult males with TARTs, most (but not all) have evidence of primary testicular dysfunction and infertility
  – Reduced number of viable sperm
  – Poor semen quality
  – Decreased inhibin B levels

Nebesio TD, Eugster EA. *Int J Pediatr Endocrinol*, 2010
At 11 years old: Bilateral TARTs
As a comparison, here is a normal testicular ultrasound:
At 15 years old: Bilateral TARTs

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Stage 1
Adrenal rest cells present within the rete testis

Stage 2
Hyperplasia and hypertrophy of adrenal rest cells

Stage 3
Further growth of the adrenal rest cells with compression of the rete testis

Stage 4
Induction of fibrosis and focal lymphocytic infiltrates

Stage 5
Irreversible damage of testicular parenchyma

Claahsen-van der Grinten HL et al. *Best Pract Res Clin Endocrinol Metab*, 2009
# 5 stage classification of TARTs

<table>
<thead>
<tr>
<th>Histological description</th>
<th>Reversibility</th>
<th>Treatment options</th>
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<tbody>
<tr>
<td>Presence of adrenal rests within the rete testis—not detectable</td>
<td>+++</td>
<td>____</td>
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<tr>
<td>Hypertrophy and hyperplasia of adrenal rest cells due to growth stimulating factors (e.g., ACTH, AII)</td>
<td>++</td>
<td>Optimizing glucocorticoids</td>
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<tr>
<td>Further growth of the adrenal rest cells with (reversible) compression of the rete testis</td>
<td>++</td>
<td>Optimizing glucocorticoids</td>
</tr>
<tr>
<td>Induction of fibrosis and focal lymphocytic infiltrates</td>
<td>–/+</td>
<td>Surgery?</td>
</tr>
<tr>
<td>Irreversible damage of testicular parenchyma. Parts of the tumour are replaced by adipose tissue</td>
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Treatment of TARTs

1) Intensifying glucocorticoid regimen in an attempt to improve biochemical control of CAH
   • Increasing the glucocorticoid dose
   • Changing to a longer-acting glucocorticoid
   • Compliance with mineralocorticoid medication may also be beneficial
   • May not improve fertility if TARTs are advanced and at a later stage

2) Testis-sparing surgery (and/or testicular biopsy)
   • Unsure if it prevents further testicular damage – often the damage is permanent and irreversible
Surveillance guidelines

- Clinical practice guidelines from the Endocrine Society:
  
  “We suggest that males with classic CAH be periodically screened from adolescence for testicular adrenal rest tumors by ultrasound”

  Speiser PW et al. *J Clin Endocrinol Metab*, 2010

- How often should screening be done?
- Why not screen in childhood?
- Is surgery a reasonable optional?
What about non-classic CAH?

- Seems to be a lower risk of fertility problems compared to men with classic CAH
- Not well studied
- There are reports of TARTs occurring in males with non-classic CAH
Other causes of reproductive problems in males with CAH

- Primary testicular failure (TARTs)
- Suppression of the hypothalamic-pituitary-gonadal axis due to high levels of adrenal sex steroids
- Obesity and increased body mass index (BMI)
- Overtreatment with glucocorticoids
Hypothalamic-Pituitary-Gonadal Axis

- Hypothalamus:
  - Gonadotropin releasing hormone (GnRH)

- Pituitary:
  - Luteinizing hormone (LH)
  - Follicle stimulating hormone (FSH)

- Testicle:
  - Testosterone from Leydig cells
  - Sperm from Sertoli cells

Inhibin B
Summary

• Fertility in men (as well as women) with CAH is reduced

• The major cause of decreased fertility in men with CAH is due to TARTs

• Early detection of TARTs and improved compliance may help to reduce the risk of infertility in males with CAH