Males with CAH – specific focus on fertility

2016 Congenital Adrenal Hyperplasia Patient & Family Summit

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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

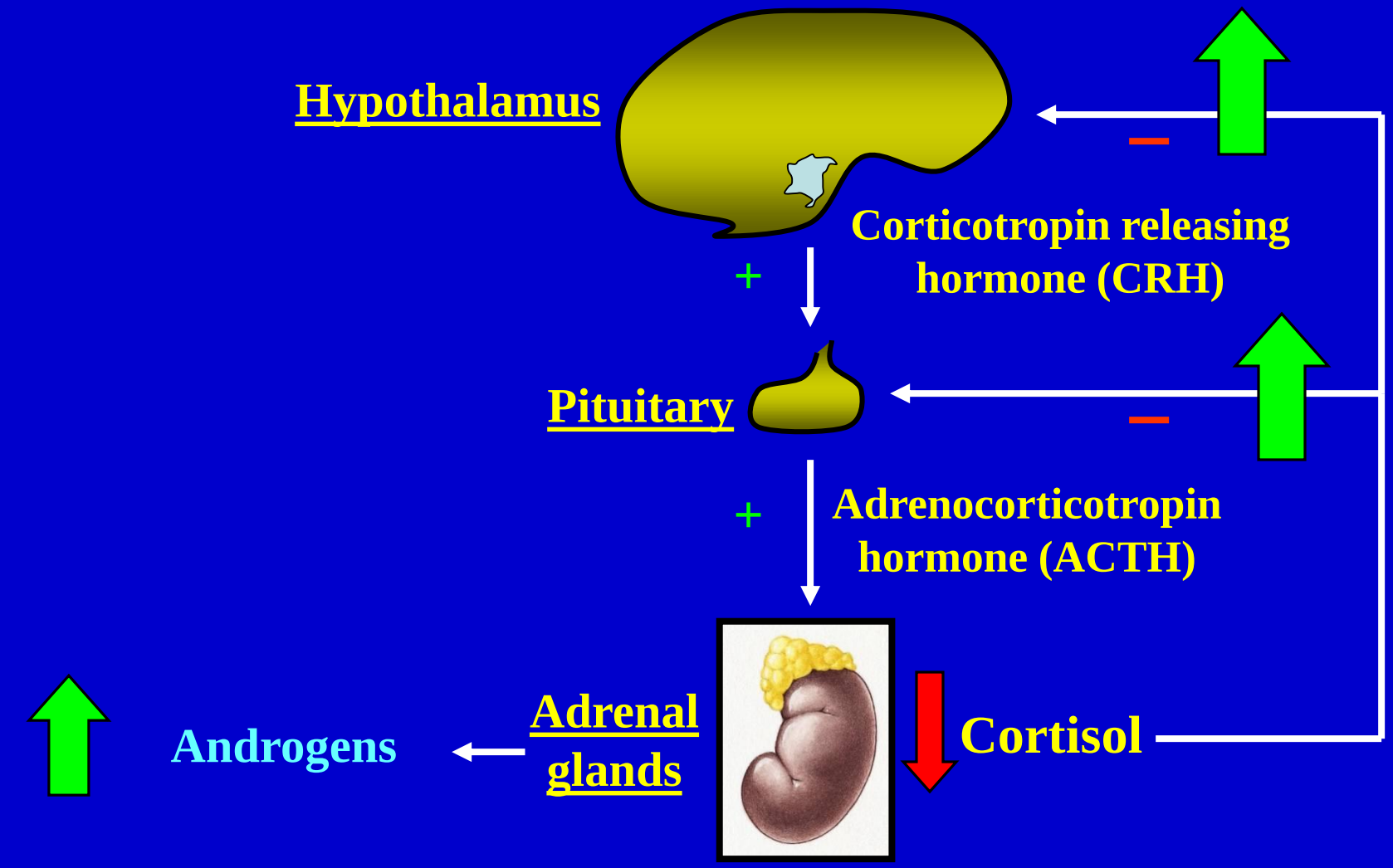
TARTs in males with CAH

- 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

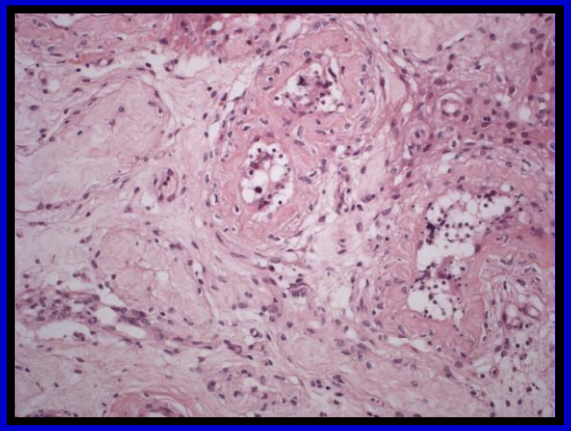
Hypothalamic-Pituitary-Adrenal Axis



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**

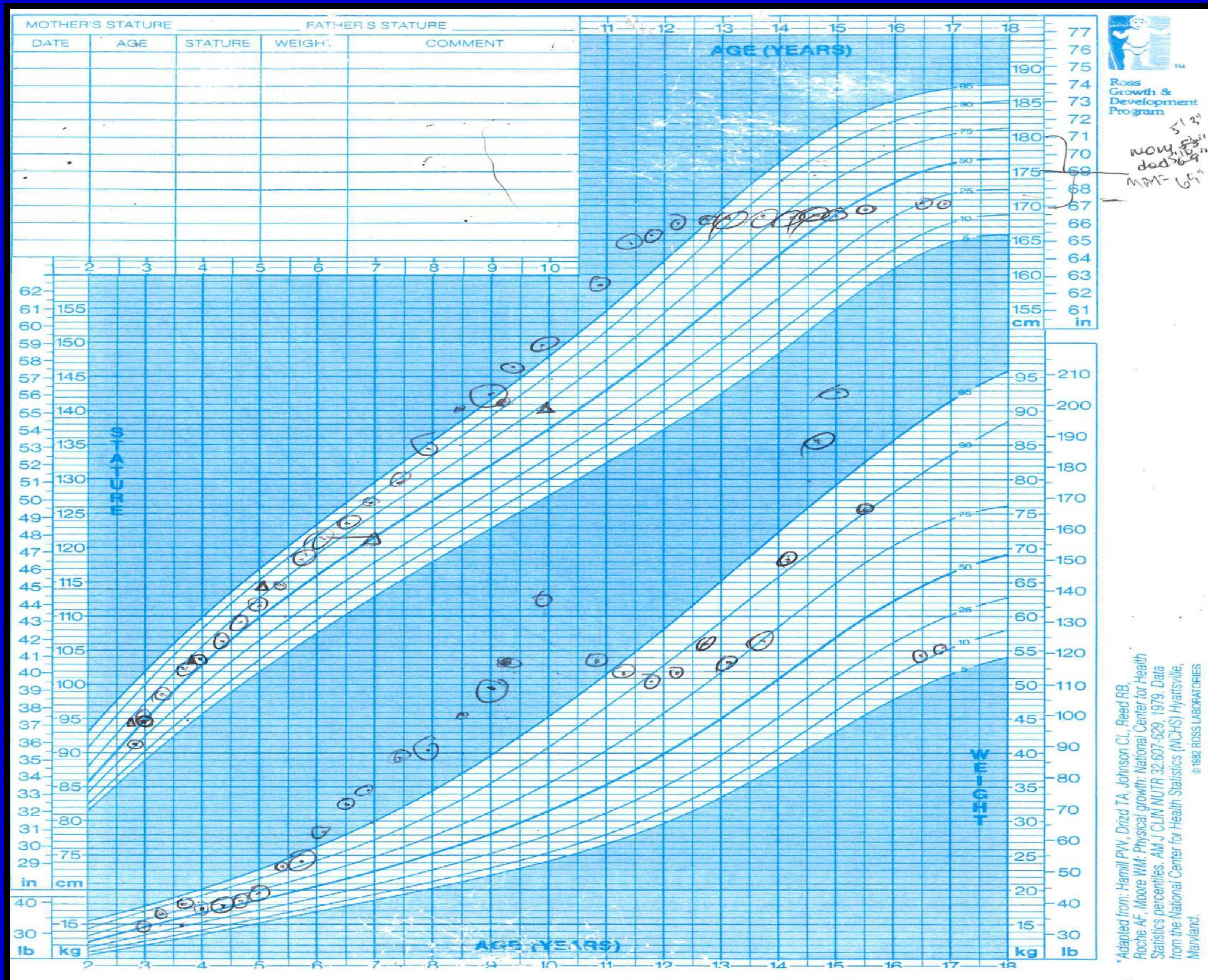


TARTs and reduced fertility

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

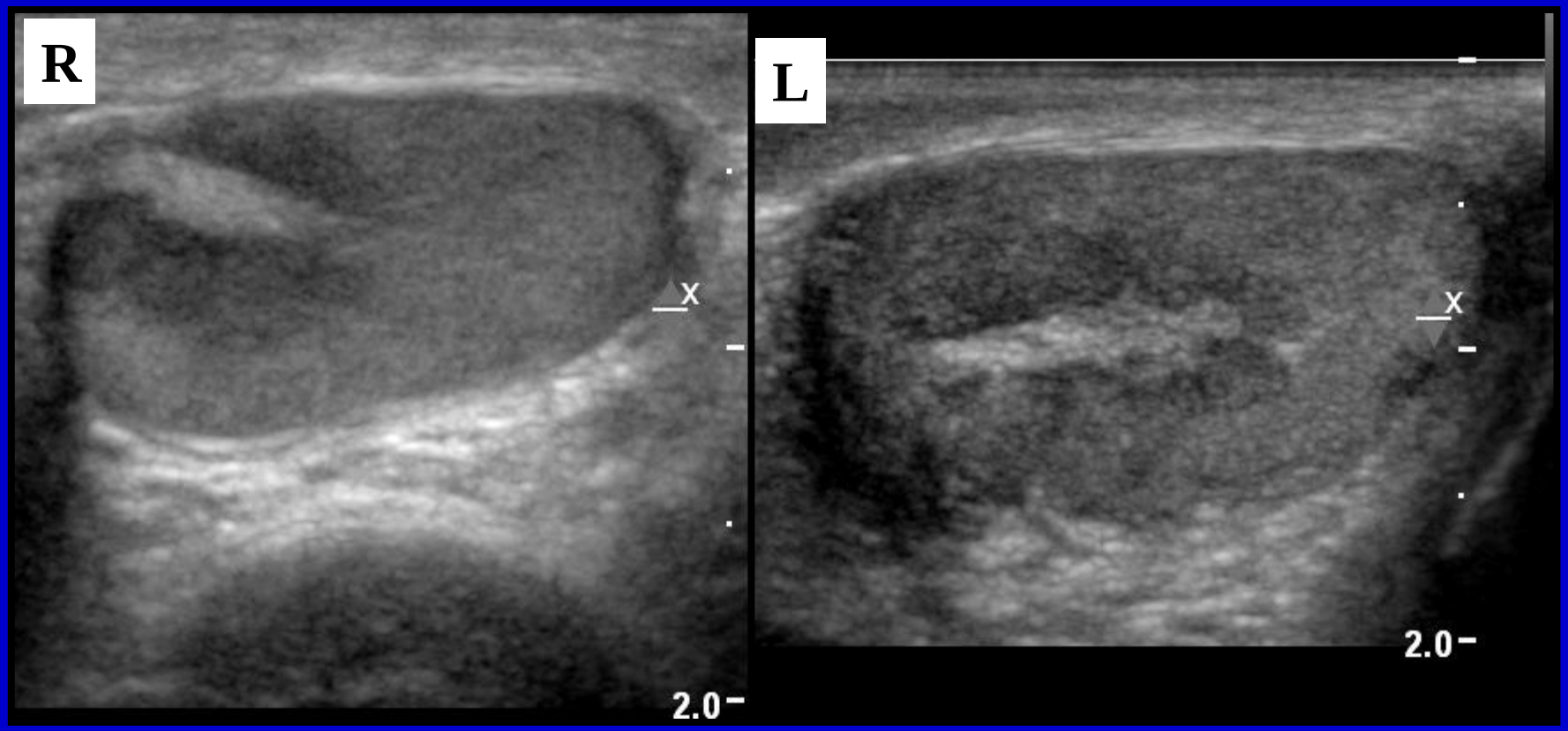
- **In adult males with TARTs, most (but not all) have evidence of primary testicular dysfunction and infertility**
  - **Reduced number of viable sperm**
  - **Poor semen quality**
  - **Decreased inhibin B levels**

Nebesio TD, Eugster EA. *Int J Pediatr Endocrinol*, 2010

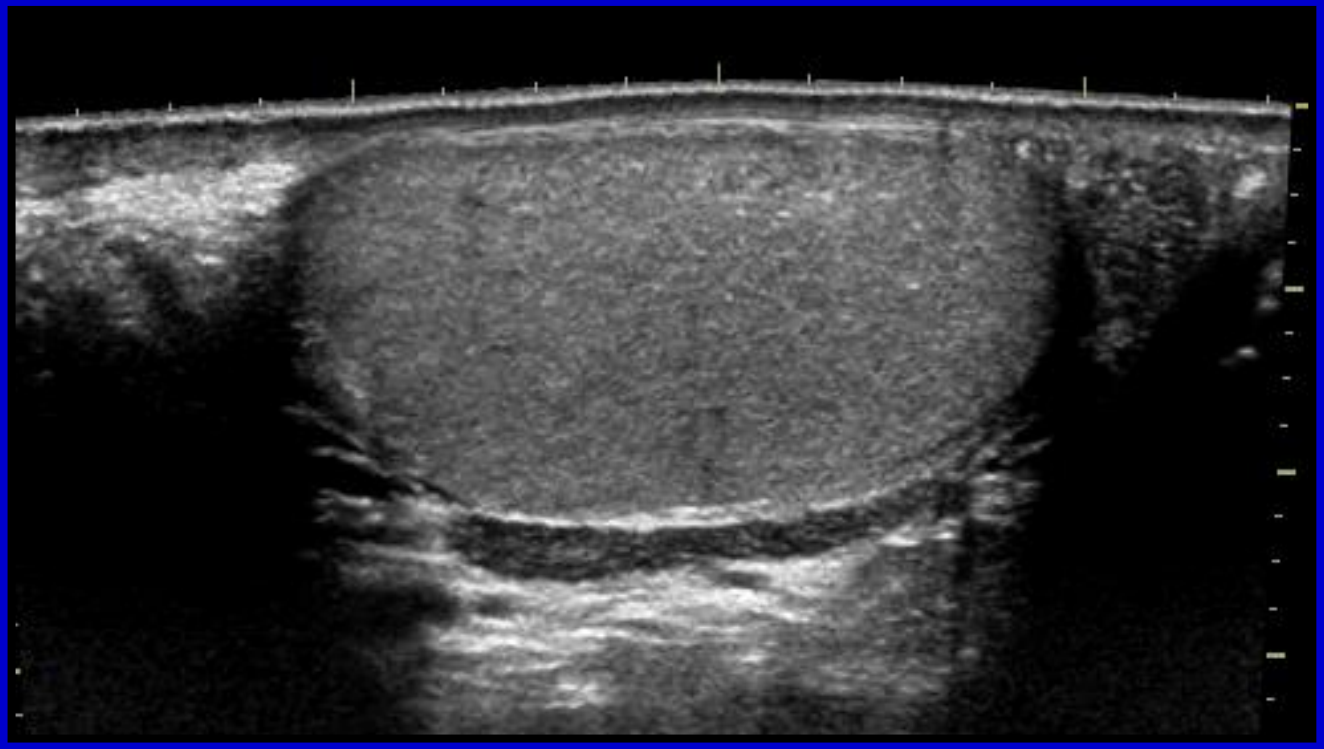


MOTHER'S STATURE
FATHER'S STATURE
DATE
AGE
STATURE
WEIGHT
COMMENT
AGE (YEARS)
STATURE
WEIGHT
cm
in
kg
lb
Ross Growth & Development Program
*Adapted from: Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM: Physical growth: National Center for Health Statistics percentiles. AM J CLIN NUTR 32:607-629, 1979. Data from the National Center for Health Statistics (NCHS) Hyattsville, Maryland.
© 1982 ROSS LABORATORIES

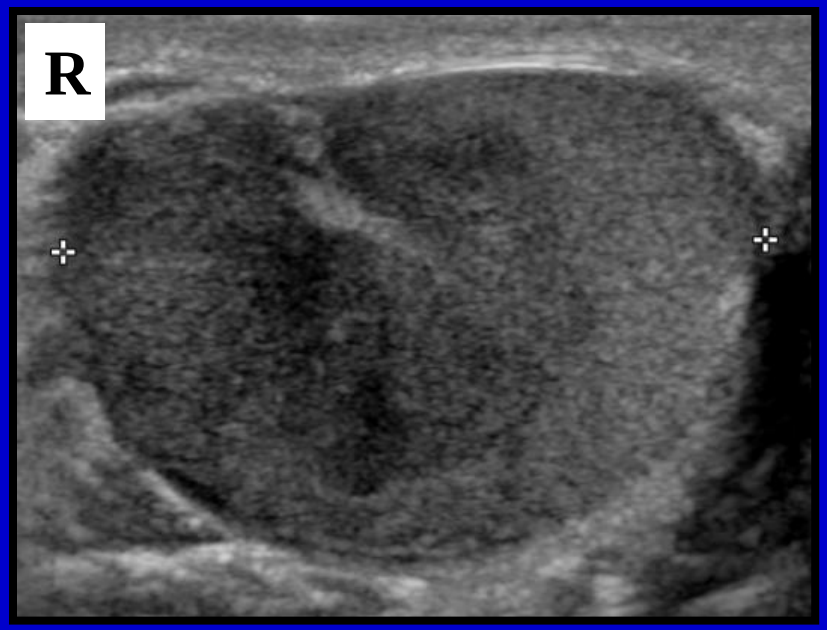
At 11 years old: Bilateral TARTs

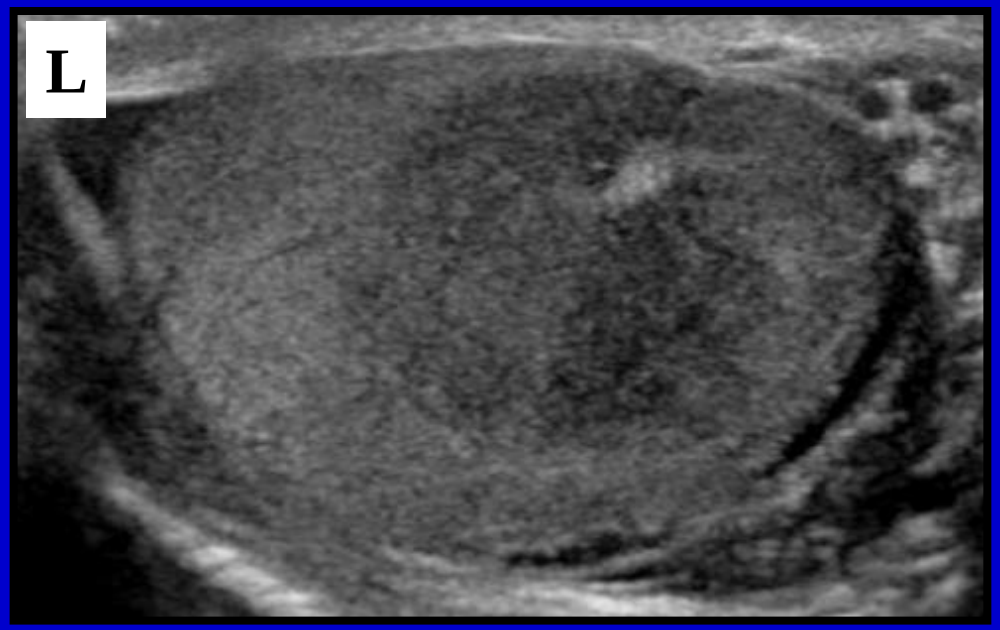


As a comparison, here is a normal testicular ultrasound:



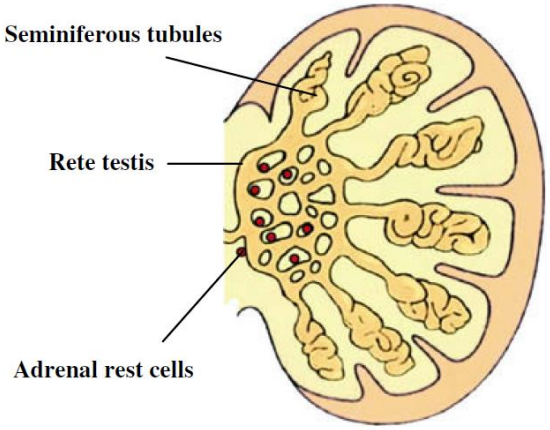
At 15 years old: Bilateral TARTs





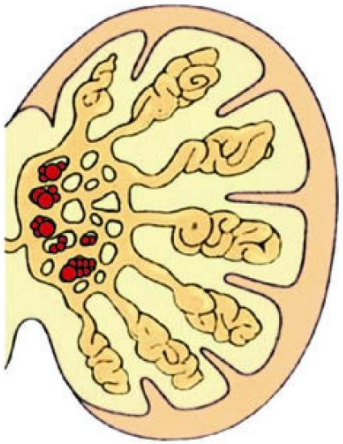
Stage 1

Adrenal rest cells present within the rete testis



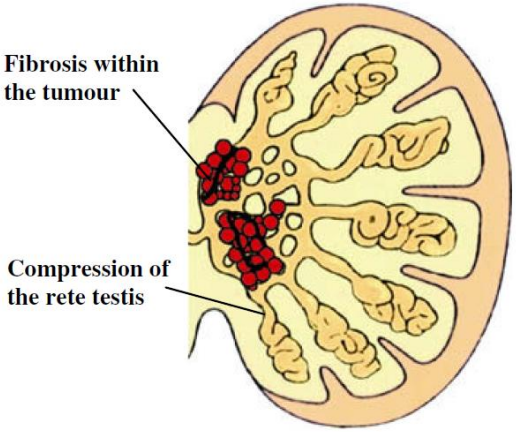
Stage 2

Hyperplasia and hypertrophy of adrenal rest cells



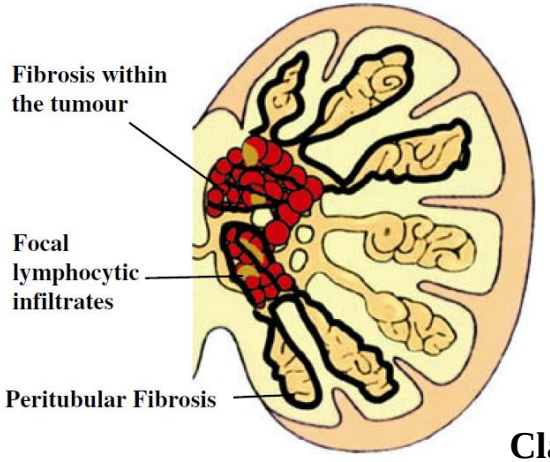
Stage 3

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



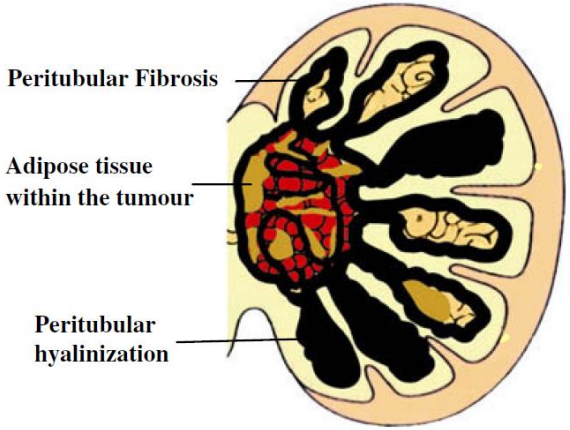
Stage 4

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

	Histological description	Reversibility	Treatment options
Stage 1	Presence of adrenal rests within the rete testis—not detectable	+++	—
Stage 2	Hypertrophy and hyperplasia of adrenal rest cells due to growth stimulating factors (e.g., ACTH, AII)	+++	Optimizing glucocorticoids
Stage 3	Further growth of the adrenal rest cells with (reversible) compression of the rete testis	++	Optimizing glucocorticoids Surgery?
Stage 4	Induction of fibrosis and focal lymphocytic infiltrates	−/+	Surgery?
Stage 5	Irreversible damage of testicular parenchyma. Parts of the tumour are replaced by adipose tissue	−	—

Claahsen-van der Grinten HL et al. ***Int J Pediatr Endocrinol*****, 2009**

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?**

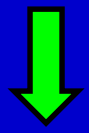
What about non-classic CAH?

- 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

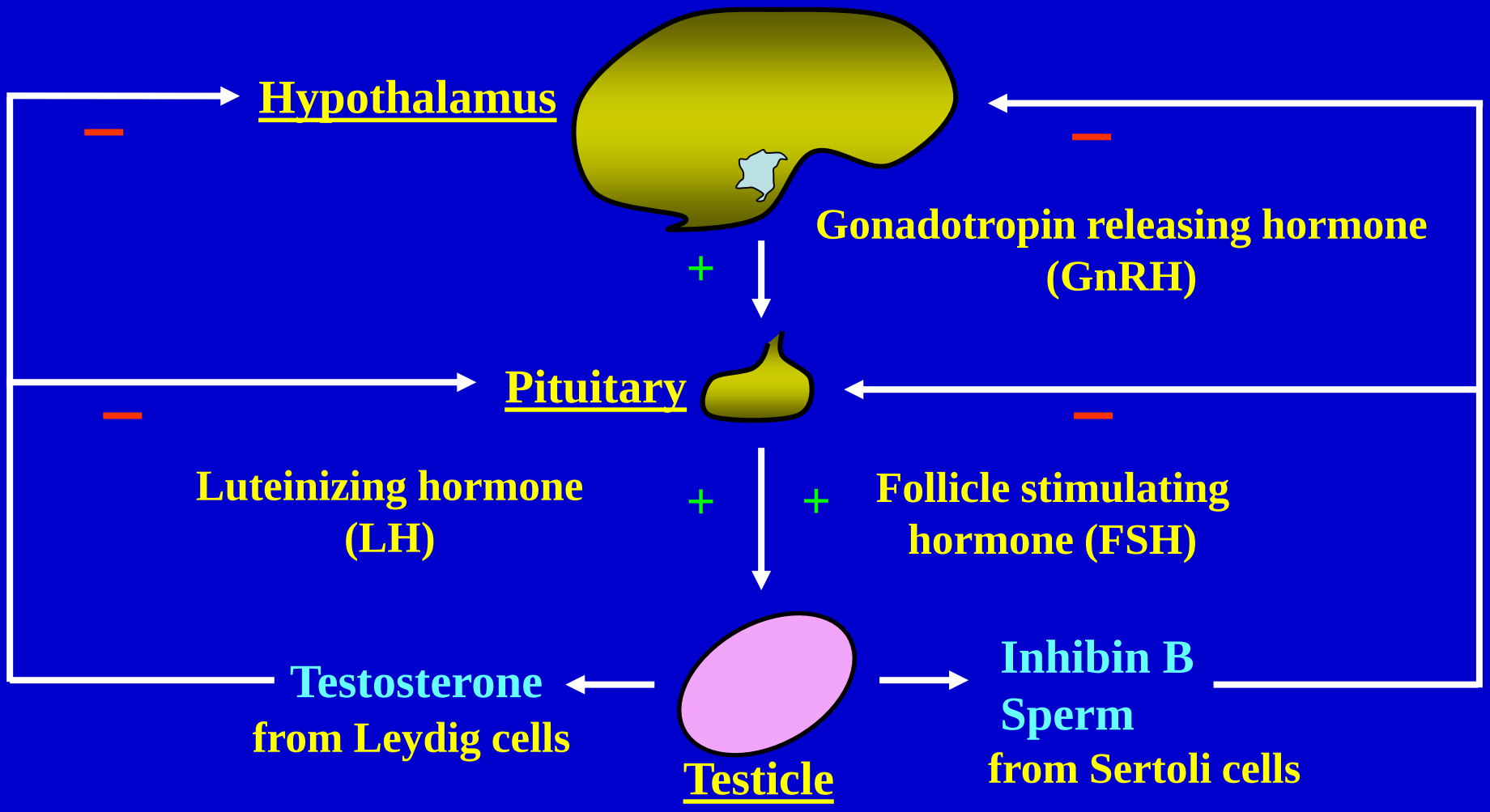
↑↑↑ androgens



↑↑↑ estrogens

- Obesity and increased body mass index (BMI)
- Overtreatment with glucocorticoids

Hypothalamic-Pituitary-Gonadal Axis



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**