

# Endocrine Issues Related to X and Y Chromosome Variations

And a few Rocky mountain wildflowers

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Children's Hospital Colorado  
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## Topics

- Hypogonadism (testosterone deficiency)
  - Physiology and cause
  - Benefits and disadvantages of testosterone therapy
  - Timing
  - Treatment options
- Small penis
- Gynecomastia
- Other hormonal abnormalities in KS
- Whatever else you want to talk about



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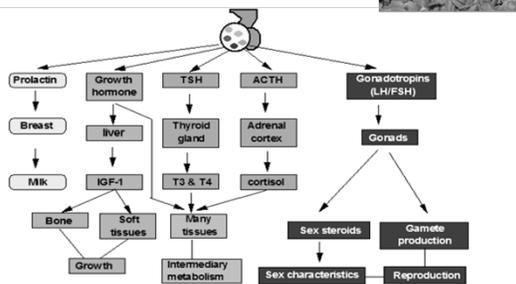
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## Pituitary Hormones



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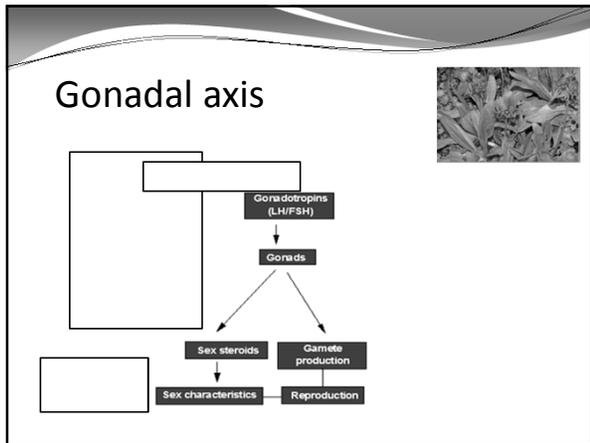
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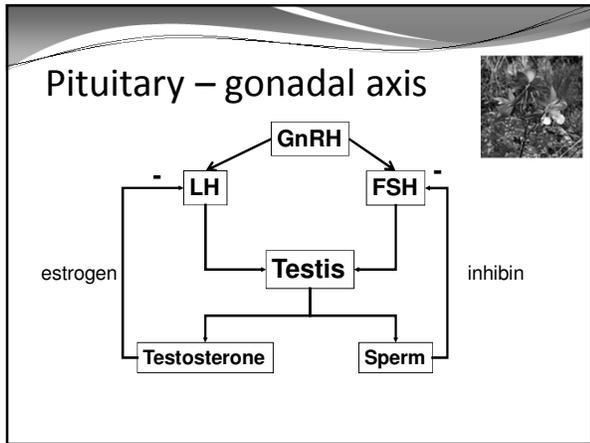
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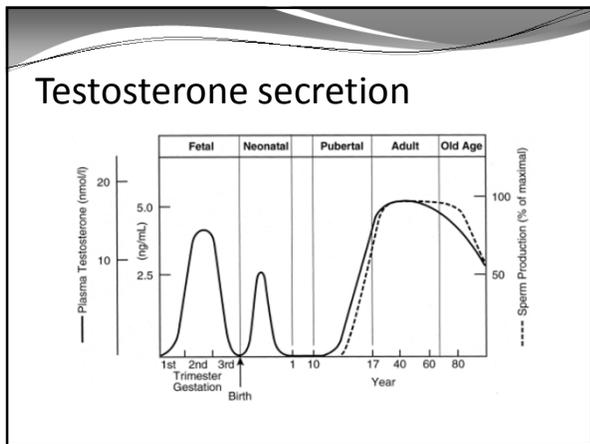
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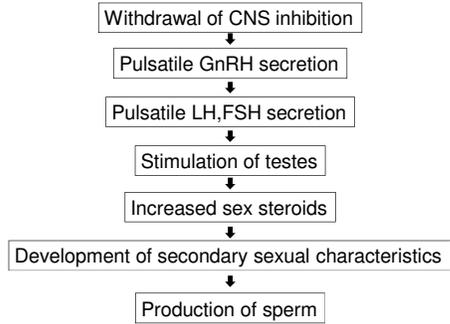
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## Normal Puberty



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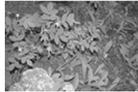
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## Pituitary –gonadal axis



- Axis is functional at birth
  - LH, FSH, and testosterone levels similar to young adults
- Axis is quiet during childhood – latency
  - Mechanism unknown
  - LH, FSH and testosterone very low
- Axis slowly activates at puberty
  - LH rises at night initially
  - Pulses of LH become larger and more frequent
  - Mechanism unknown

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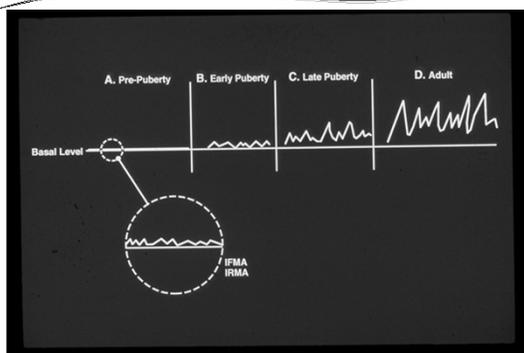
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LH pulsatility during pubertal onset

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## Signs of Puberty (Boys)

- Testicular enlargement (>3 ml) 11.8 years
- Pubic hair 12 years
- Penile enlargement 13 years
- Growth acceleration 14 years  
(peaks in latter half of puberty)

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## Adrenarche

- Increase in adrenal androgen production (DHEA, DHEA-s, androstenedione)
- Usually at same time of puberty but not always
- Manifest with acne, oily skin, axillary hair, pubic hair
- No testicular enlargement
  - May be difficult in KS, though most boys will have some testicular enlargement at puberty

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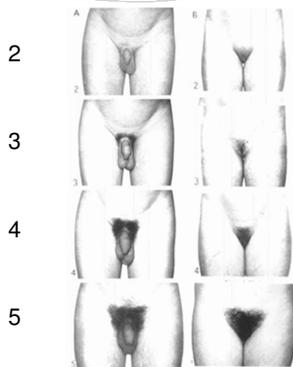
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## Tanner Staging (Pubic Hair)



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## Pubertal Onset (Boys)

- Testicular enlargement >3 ml
- Age range 9-14 years



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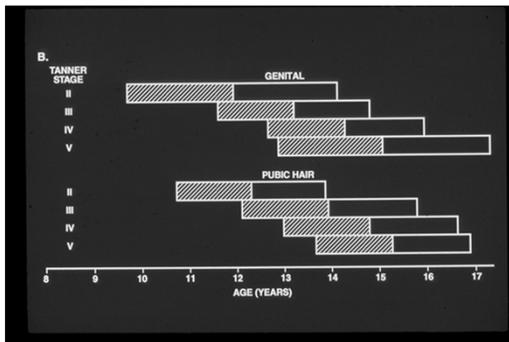
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Tanner Stages vs Age - Boys

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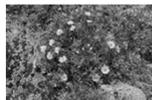
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## Hypogonadism in KS



- Primary testicular failure
  - Central hormones responsible for onset of puberty are normal
  - The testis itself is abnormal and unable to respond appropriately to LH and FSH

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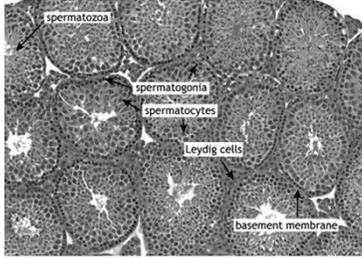
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## Normal Testis



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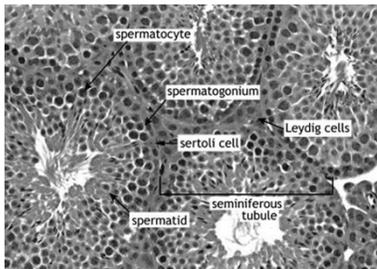
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## Normal Testis



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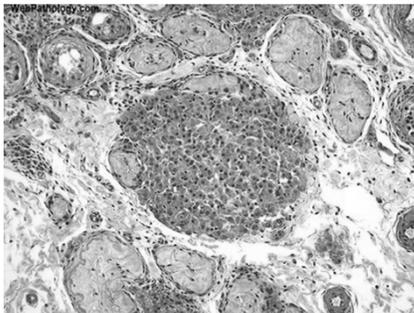
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## Klinefelter testis



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## Hypogonadism in KS



- Once "pituitary puberty" starts
  - Pituitary attempts to drive response from the testis
    - Sperm cell production abnormal – FSH rises
    - Testosterone production abnormal – LH rises
- Hypergonadotropic hypogonadism
- LH and FSH won't be elevated prior to puberty
  - Bone age

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## Bone age



- A means to determine degree of development
- Puberty generally starts at a bone age of 12 in boys
- Bone age is a better predictor of puberty than chronological age
- LH and FSH are expected to rise only after bone age (biological age) has reached an appropriate development
- Bone age delay does not diagnose anything
- Bone age indicates the remaining growth potential

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## Bone Age



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## Timing of testosterone therapy

- **Early or late childhood?**
  - Small penis
  - Behavioral benefits?
  - Physical benefits of low doses?
    - Theoretical based on low doses present in typical boys
- **Age driven**
  - Normal time of puberty in boys – 12 to 12.5 years
- **LH driven**
  - Start testosterone when LH begins to rise
  - Indicates that the pituitary is trying and failing
- **Gynecomastia – breast development in males**

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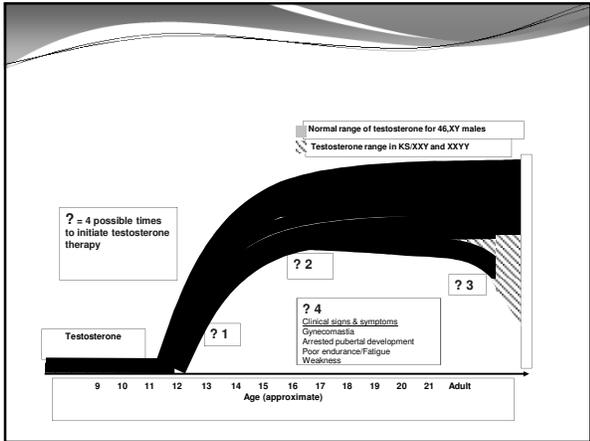
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## Small penis

- Normal penis – wide range
  - > 2.5 cm in length and 1 cm in diameter
- The penis may be small due to inadequate testosterone production in utero or in early childhood
- Short courses of low-dose testosterone may be used to promote penile enlargement
- Therapy is not required except for cosmetic purposes
  - No evidence of effect on adult penis size
  - May need to get repeated due to regression
- Depot testosterone 25 mg injection once a month for 3 months

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## Sex Steroids and Breast Development

- Hormonal effects on breast development
  - Estrogens stimulate breast development
  - Androgens inhibit breast development
- Breast development thought to reflect increases in E/T ratio
  - decreased T
  - increased E
  - change in conversion rate

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## Gynecomastia – causes of abnormal E/T ratio

- Slow rise in testosterone fails to keep up with early estrogen in boys with gonadal abnormalities
- Increased LH promotes estrogen secretion preferentially
- adrenal androstenedione production a precursor for estrogen
  - Decreased testosterone production early doesn't balance

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## Consequences of Testosterone Deficiency

- reduced body hair
- decreased muscle mass and strength
- increased fat mass & altered fat distribution
- unfavourable cholesterol changes (increased LDL and reduced HDL)
- decreased hemoglobin
- decreased libido, erectile dysfunction
- osteoporosis
- depressed mood

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## Benefits of testosterone

- Virilization
  - Outward signs of pubertal development
  - Promotion of normal sexual function and development
  - Maintain similarly with peers
  - Self-esteem
- Muscle development/fat distribution
- Body proportions – reduction in excess limb length
  - Testosterone promotes bone maturation
  - Testosterone promotes spine growth
- Bone maturation and mineral accumulation
- Prevention/treatment of gynecomastia
- Behavior?

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## Disadvantages of testosterone

- Acne
- Increased sexual activity
- Increased strength
- Short stature if started too early or titrated too fast

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## Options for testosterone therapy

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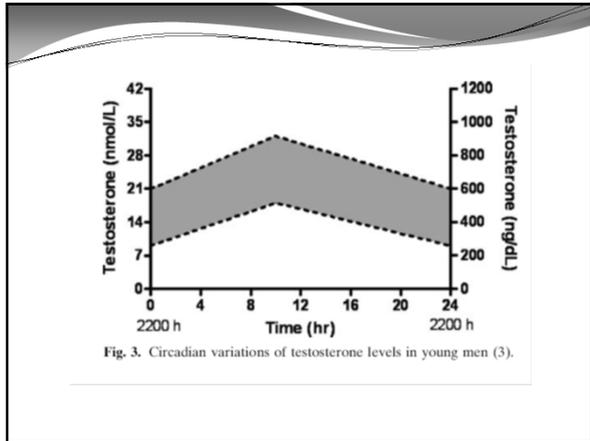
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### Oral Testosterone



- Not used extensively in the US
- Concern for liver pathology
- May be less of a concern with more modern agents, but pediatric endocrinologists are cautious

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### Injected testosterone



- Testosterone enanthate or cypionate in oil
- Given every 2-4 weeks
- Benefits
  - Supervised injections
  - Inexpensive
  - Don't have to fuss with it
- Disadvantages
  - Effect may be inconsistent over the month
  - Requires an injection

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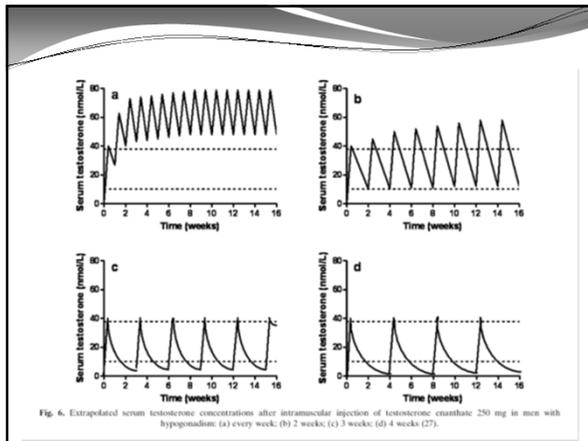
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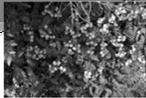
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## Injected testosterone



- Starting dose
  - Prepubertal – 75 mg once a month
  - Pubertal 150-200 mg once a month
- Titration
  - Adult dose is 200 mg every 2-4 weeks
  - Titrate to adult dose over 3-4 years (every 12 months or so)
- Adult dose determination
  - Serum testosterone levels – peak or trough?
  - subjective

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## Transdermal testosterone

- Patch
  - 2.5 or 5 gram patches –
    - Adult dose 2.5 – 10 grams a day
  - Changed daily
  - More consistent than injections
  - Doses fixed
  - Have not been well received in general
    - Itchy
    - Fall off
    - visible




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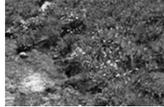
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## Transdermal testosterone

- Gel
  - Fixed dose pack or pump
  - Applied daily
  - More consistent than injections
  - Disadvantages
    - Daily application
    - Messy for some boys
    - May require parental assistance
    - Concern over transfer of testosterone to others



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## Other

- Buccal
  - Applied to the lining of the mouth
- Implants
  - Placed every 3-4 months by minor surgical insertion
  - Dosing remains uncertain
- Depot testosterone
  - Injected every 3-4 months
  - Delivery designed to be more consistent than monthly injections



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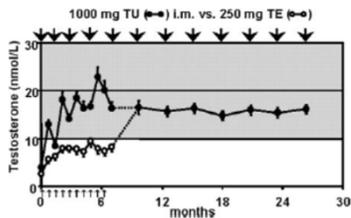


FIG. 2. Serum T levels (mean  $\pm$  SEM) during the whole study period (up to 30 months of therapy). After 30 wk of therapy, all patients switched to TU injected every 12 wk.

Schubert M et al. J Clin Endocrinol Metab 89:5429-5434, 2004

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## Monitoring of therapy



- Serum testosterone
  - Injections – trough or peak
  - Subjective
- Gel
  - Morning testosterone 1 month after a dose change
  - Twice a year when on stable dose

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Does testosterone help with behavioral difficulties, mood, speech, learning, or motor skills in XXY?

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## Psychological Effects of Testosterone therapy in XXY

- Nielsen, J., et al, *Follow-up of 30 Klinefelter males treated with testosterone.* Clin Genet, 1988. 33(4): 262-9.
- **Results: Improvements in mood, attention, and social relationships following testosterone treatment**
- Patwardhan, A., et al, *Brain morphology in Klinefelter syndrome: extra X chromosome and testosterone supplementation.* Neurology, 2000. 54(12): p. 2218-23.
- **Treated group (n=5) had increased verbal fluency scores and increased temporal lobe gray matter compared to untreated group (n=5)**
- Heuser, et al, *Androgen replacement in a 48, XXYY male patient.* Arch Gen Psych, 1999. 56(2): p. 194-5.
- Sourial, N. & F. Fenton, *Testosterone treatment of an XXYY male presenting with aggression: a case report.* Can J Psych, 1988. 33(9): p. 846-50.
- **Conclusions: Improvements in aggressive behavior and mood after initiation of testosterone in XXYY**

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## Current studies:

- Dr. Judith Ross at Thomas Jefferson University
  - NIH funded study on low-dose oral androgen replacement in young males (age 4-13) with XXY
  - Double-blinded
  - Study is no longer enrolling and results will be published in 2012.

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## Pilot study at Children's Hospital Colorado

- Inclusion Criteria:
  - 12-21 year old males with XXY, XXYY, XXXY
  - Starting on testosterone replacement therapy
- Recruitment from:
  - Children's Hospital Colorado, Denver
    - eXtraordinary Kids Clinic
  - National Advocacy Organizations
    - Klinefelter syndrome & Associates (KS&A)
    - The XXYY Project

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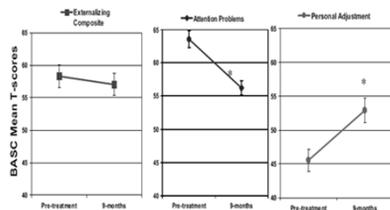
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## AIMS / HYPOTHESES

**Specific Aim:** To Identify psychological, behavioral, and motor changes in males with KS/XXY, XXYY and XXXY before and after 12 months of testosterone treatment.



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## NEXT STEPS:

- Placebo-controlled trial of testosterone gel started in early puberty in adolescents with XXY
- Children's Hospital Colorado, eXtraordinarY Kids Clinic
- Principal Investigator: Nicole Tartaglia, MD
  - Co-investigators:
    - Phil Zeitler, MD, PhD
    - Bruce Bender, PhD (psychologist)
    - Richard Boada, PhD (psychologist)

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## Study Protocol:

- Included: Males with XXY just starting puberty (approximately 10-14 years of age)
- 3 research visits in Denver
  - Travel costs and testosterone gel included as part of study participation
- Study visit will include:
  - Physical Examination
  - Neuropsychological testing (Cognitive skills/IQ and executive functioning)
  - Motor Skills (strength, balance, coordination)
  - Behavioral questionnaires
- Contact Susan Howell or Dr. Tartaglia for more information about the study at the eXtraordinarY Kids Clinic table in the lobby

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## Other hormonal abnormalities in KS

- Hypothyroidism

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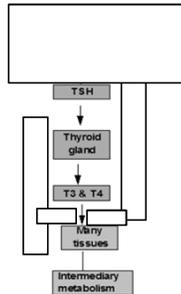
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## Thyroid axis



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## Hypothyroidism

- Primary thyroid failure
- Cause unknown
- Analogy to gonadal failure
  - Thyroid fails
  - Low T4
  - TSH rises
- Treatment easy
- Levothyroxine (T4) replacement
  - No need to replace T3 – body converts naturally
- Titrate to normal TSH

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## Other hormonal abnormalities in KS

- Diabetes
  - Generally related to excess body fat
- Low bone density
  - Vitamin D deficiency
  - Hypotonia, low muscle mass
  - Delayed testosterone replacement or testosterone deficiency
  - Overt osteoporosis (fracturing) is uncommon

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Questions?



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