# FA & Endocrine Issues

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- Most children & adults with FA have some endocrine issue
- Related to FA itself or treatment
- Persons with FA should have an annual endocrine evaluation

# Outline of talk

- Hormones by age
  - Glucose & insulin
  - Growth
  - Hypothyroidism
  - Growth hormone deficiency
  - Puberty
  - Bone mineral
- Evaluation
- Therapy

# Growth control by age

- Fetal
  - Placental nutrients
- Infant
  - Nutrition
  - Insulin
  - Thyroid
- Child
  - Nutrition / insulin
  - Thyroid
  - Growth hormone
- Adolescent
  - Nutrition / insulin
  - Thyroid
  - Growth hormone
  - Puberty hormones

# Glucose-insulin control

- Body's ability to use nutrition
  - Depends on insulin secretion
  - Insulin influences growth & health
- After intake of meal
  - Rise in glucose, then rise in insulin
- Normal glucose
  - does not rise too high
  - & does not fall too far

# Glucose-insulin effects by age

- Infant
  - Growth
  - Hypoglycemia
- Child & adolescent
  - Growth
  - Hyperglycemia
- Adult
  - Diabetes
  - Cardiac health

# Weight

- Often below average (-1.5 SD)
  - but low caloric intake does not explain height deficit
  - 1/4 have low weight for height (called “failure to thrive”)
- 1/4 to 1/3 -- relatively overweight for height

# Factors affecting weight

- small appetite
- malabsorption
- increased calorie needs during illness
- With low insulin secretion
  - blood sugar rises, lose glucose in urine
  - insulin deficiency contributes to poor weight gain.

# Impaired insulin secretion (Elder 2008)

- Findings on oral glucose tolerance test
  - 8% of 39 with FA -- diabetic
  - 46% -- impaired glucose tolerance
  - Insulin
    - fasting levels low
    - sluggish initial insulin secretion
    - 72% -- later high insulin after glucose
  - consistent with beta cell dysfunction

# Glucose/ Insulin

- Limited rapid insulin rise to food
  - Is an inherent feature of FA
- Worse after androgen or steroid therapy, or after HCT
- Leads to
  - impaired glucose tolerance, poor growth, overt diabetes mellitus.

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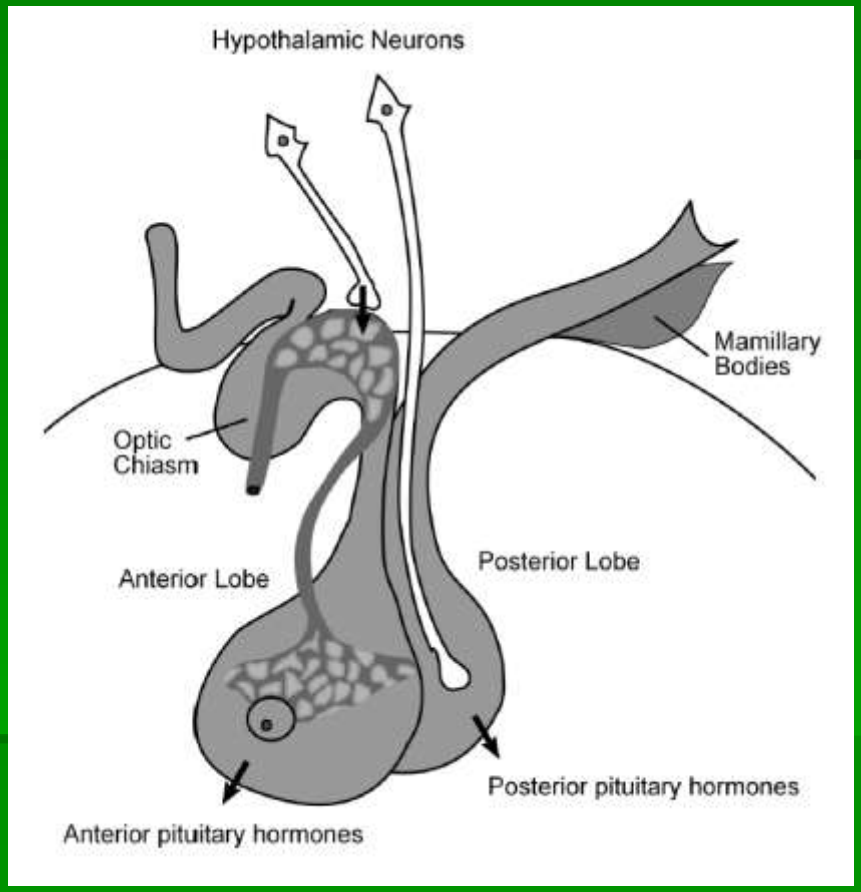
# Height in FA

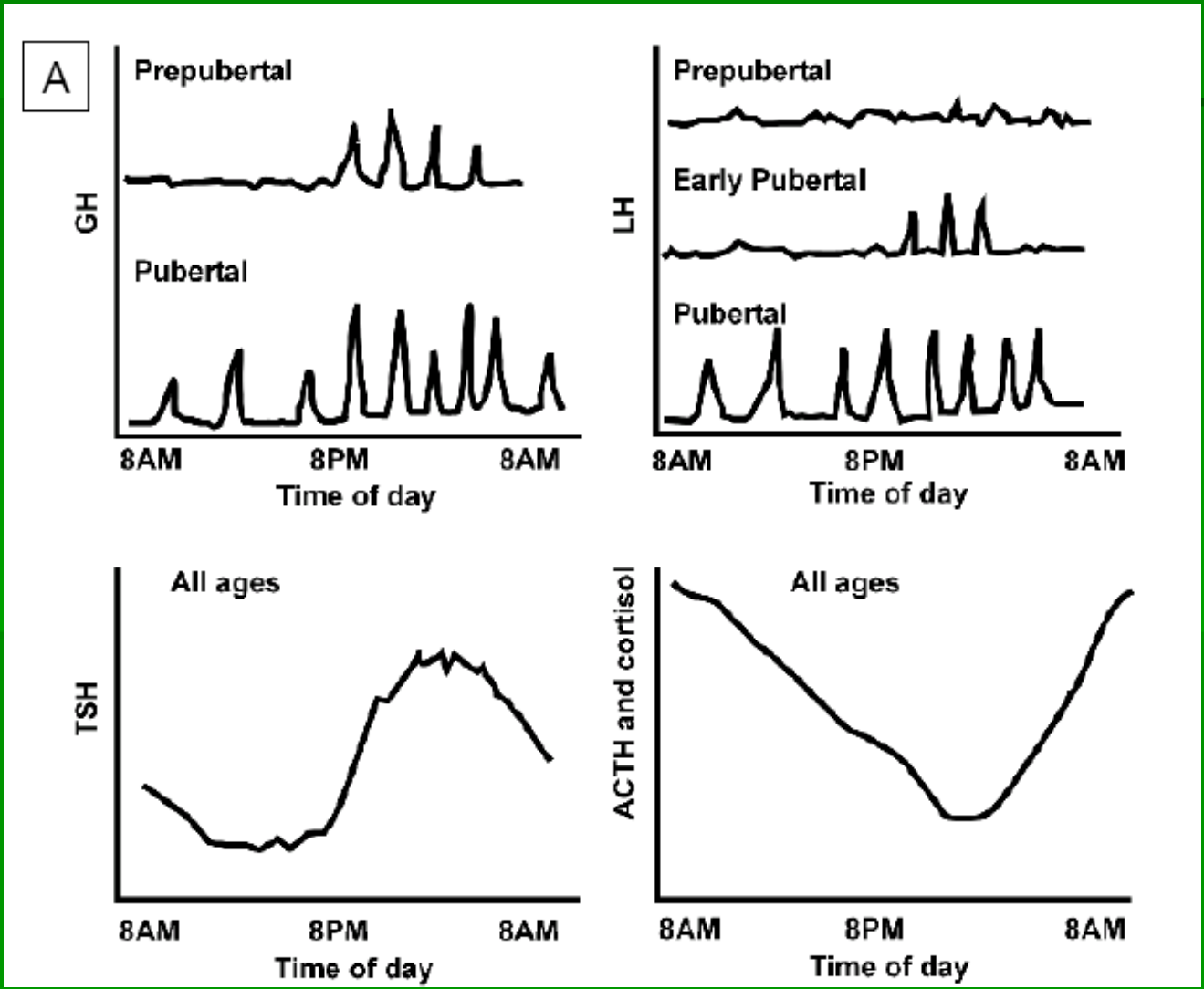
- Average height -- 1st percentile
  - Women -- 150cm, 4 ft 11 in
  - Men -- 161cm, 5 ft 3.5 in
  - Half have height within normal range.
- Taller than average – 10%

# Hypothalamic pituitary function




Pituitary releases GH, TSH, LH, FSH, ACTH, Prolactin, Vasopressin

# Patterns of hormones



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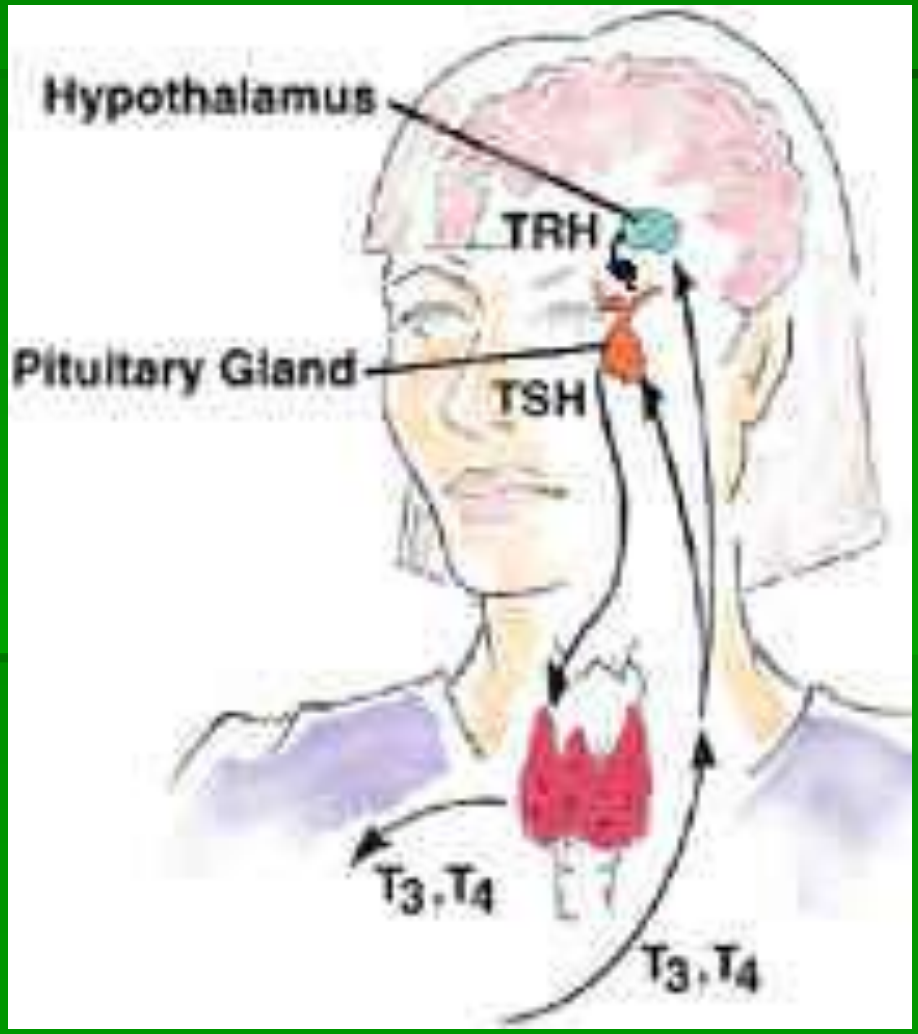
# Thyroid control



# Thyroid effects by age

- Infant / toddler (< 3y)
  - Brain development, intellect & growth
- Child & adolescent
  - Growth & puberty
- Adult
  - Metabolism & energy

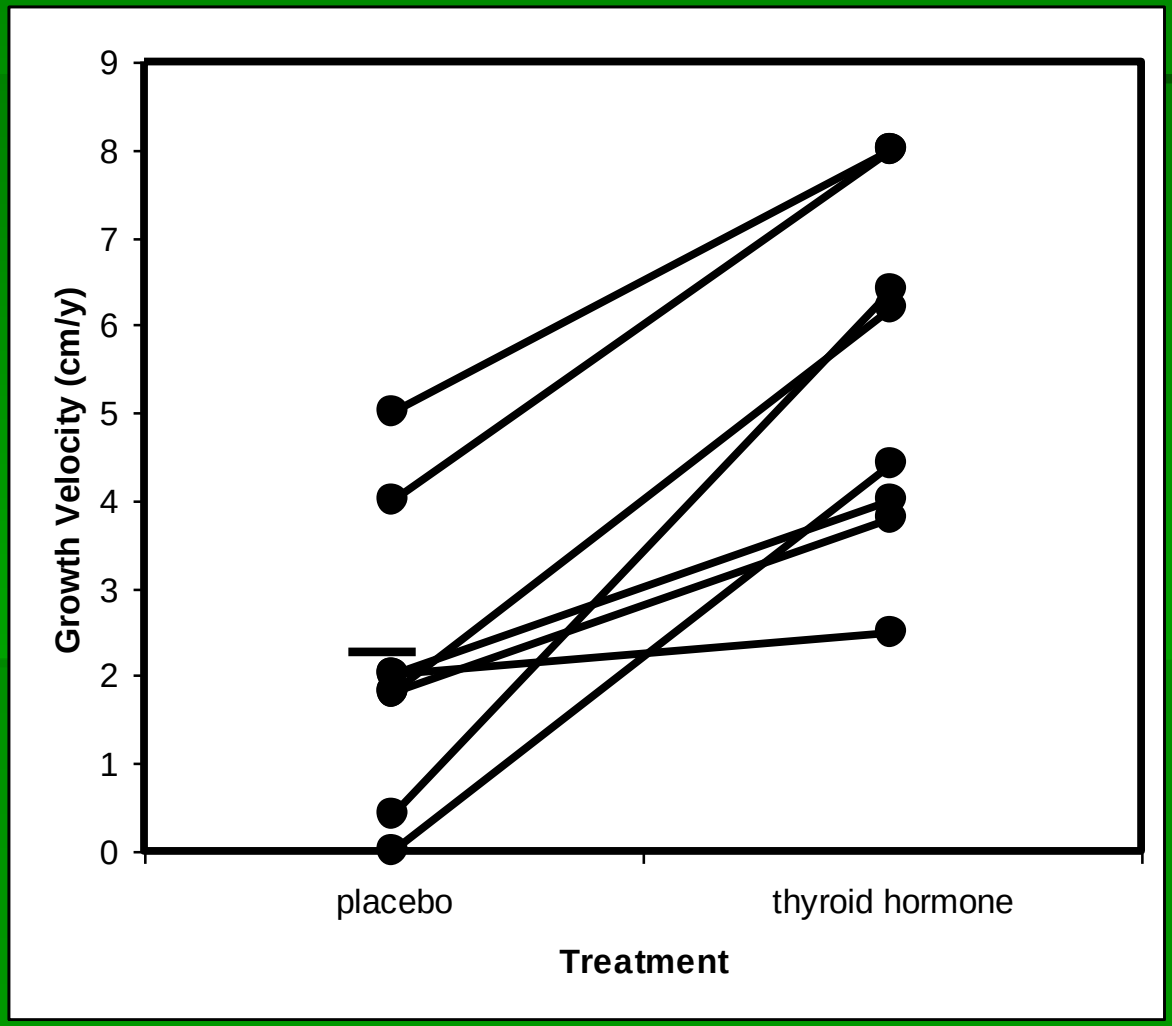
# Hypothyroidism

- Thyroid hormone levels in FA are mildly abnormal
  - borderline low T4 or FT4
  - borderline high TSH, values >3 are suspicious

# Thyroid Study (Eyal 2008)

- supported by FARF
- Eight children with FA
  - TSH > 3 mU/L or FT4 in lowest 1/3 of normal range
  - treated for 7mo with thyroid hormone, 7mo with placebo
- Growth rate faster on thyroid hormone than on placebo
- Conclusion:
  - T4 therapy of FA children with borderline TFT's may improve their growth

# Growth Velocity (GV) during placebo & thyroid therapy (8 children with FA)




Eyal 2008

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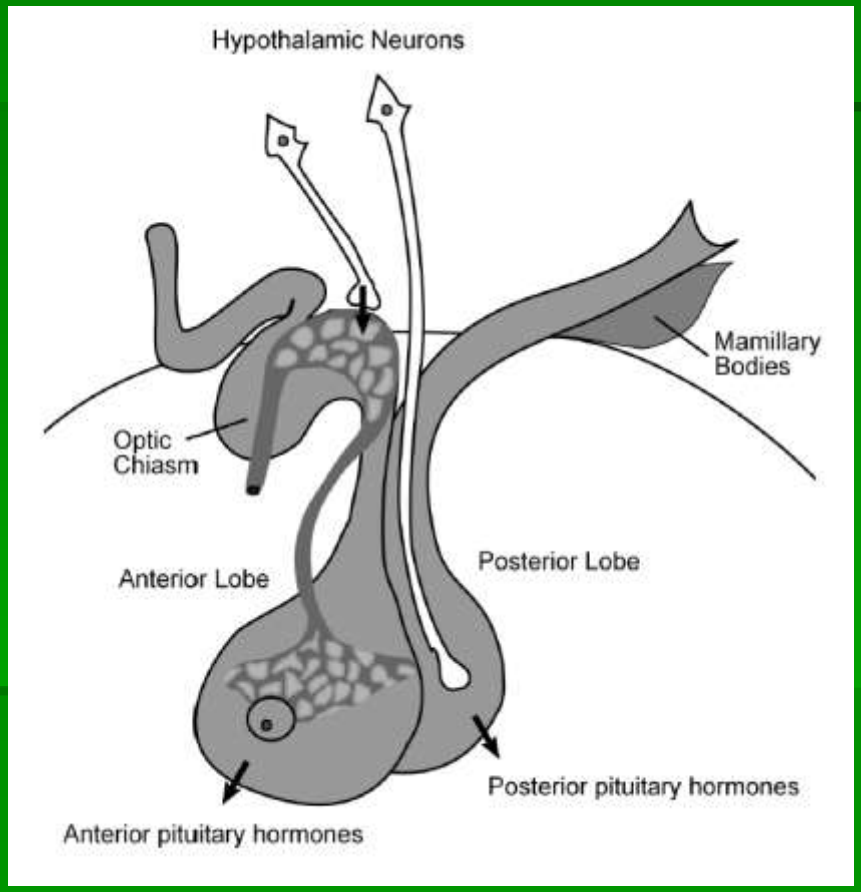


GH stimulates IGF-I action on bones & muscles

# GH by age

- Infant
  - GH not as important
- Child & adolescent
  - Growth
  - Muscle strength
- Adult
  - Bone mineral density
  - Muscle strength
  - Lipid health

# GH Deficiency (GHD)

- Only a few patients with FA have GHD
- 30-40% have low GH peak
  - But sometimes not short, or growing OK
- GH levels often low overnight
  - "partial" GHD?
- GH & IGF-I are not as low as height.

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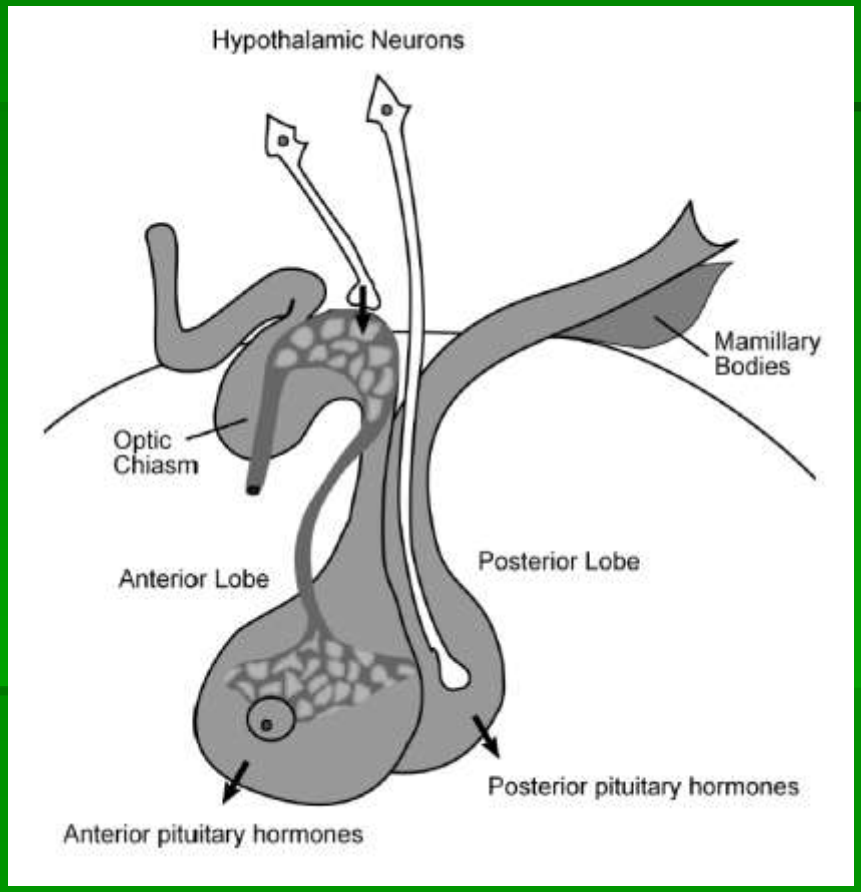
# Puberty hormone control




Pituitary LH & FSH stimulate ovaries / testes

# Puberty hormones by age

- Infant
  - Temporary activation
- Child
  - Inactive
- Adolescent
  - Active hormones
- Adult
  - Sexual function

# Puberty

- Early onset of puberty
  - decreases time to grow taller
  - before age 8y in girl & 9y in boy
- Delay defined as
  - no puberty in 12y girl or 13y boy
  - no menstrual period yet in 14y girl.

# Androgen therapy

- Criteria for androgen use in FA
  - determined by hematologist or transplanter
- Androgens
  - speed up growth
  - improve blood counts
  - virilize both boys & girls
  - mature bones faster
  - shorten period of time to grow
- BA advance may exceed gain in height
  - recheck BA every 6 months

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# Bone mineral control

- Nutrition, vitamin D, calcium
- Growth hormone
- Puberty hormones

# Bone mineral by age

- Infant & child
  - Gradual increase
- Adolescent
  - Rapid rise in bone mineral
- Adult
  - Peak bone mineral in about age 25y
  - Then gradual decline

# Bone Mineral Density (BMD)

- Only 2 articles about BMD in FA
  - 13 adults (NIH)
    - Most had osteopenia or osteoporosis compared to normal for gender & age
  - DXA overestimates incidence of osteopenia in small stature
    - Need to adjust for height age?

# BMD in FA (Rutter & Rose, 2008)

- Our findings
  - BMD in FA is normal
  - both before & after transplant (BMT)
  - if adjusted for height
- Encourage adequate vitamin D & calcium intake

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# Annual evaluation

- Accurate height measurement
- 8am TSH, T4, FT4, cortisol
- OGTT, or glucose & insulin after eating
- Other
  - GH stimulation tests, BA
    - If on thyroid therapy & growth is slow
  - MRI of head
    - If multiple deficiencies
  - LH, FSH, estradiol or testosterone
    - If delayed puberty

# Therapy, Diet

- adequate calories & regular exercise
- sufficient calcium & vitamin D
- avoid concentrated sweets
  - complex carbs vs simple sugars
  - avoid excessive sugar intake

# Insulin

- Long-acting basal insulin
  - not needed if normal fasting glucose
- Short-acting insulin at meals
  - “cover” for carbs
  - If hyperglycemia
    - Glucose >200 at 30 min after OGTT with low insulin
    - Or post-prandial glucose consistently >180mg/dL
- Check blood sugars 2H after start of meal

# Thyroid hormone

- Thyroid hormone therapy
  - If TSH over 3mU/L (primary)
  - Or if FT4 low with normal TSH (central)
- Treatment target
  - TSH 0.5 - 2.0mU/L (if primary)
  - FT4 in upper third of normal (if central)

# Growth hormone

- GH use in short child with FA
  - after HCT if child has GH deficiency
  - not just for short stature or SGA
  - Controversy
    - use of GH before HCT, or in absence of GHD
- IGF-titration
  - Adjust GH dose to keep IGF-I mid-normal

# Depot Lupron

- In short child with puberty too early
  - Suppress puberty for 3y
  - Permits time to keep growing taller

# Estrogen

- No puberty by age 13y
- In short girl
  - Low dose estrogen therapy
  - Avoid rapid increase in estrogen dose
- In normal height girl
  - slow increase in estrogen dose every 6m until adult dosing

# Testosterone

- No puberty by age 14y
- In short boy
  - Low dose testosterone therapy
  - Observe for pubertal progression for next 6m
- In normal height boy
  - Slow increase in testosterone dose every 6m until adult dosing

# Bone therapy

- Adequate dietary calcium & vitamin D
- Elemental calcium:
  - 500mg daily in young child
  - 1000 to 1500mg in adolescent
  - 1200mg in adult
- Vitamin D:
  - 1000 units daily
- Bisphosphonates
  - if BMD low with fractures

# Endocrine -- adults with FA

- Adults with FA should see endocrinologist
- Attention to
  - thyroid status
  - glucose tolerance
  - lipid abnormality
  - gonadal function
  - bone mineral density

# Summary

- Children & adults with FA have risk for
  - Weight low or high
  - Sluggish insulin release
  - Small stature
  - Hypothyroidism
  - GH deficiency
  - Early or late puberty
  - Low bone mineral after long steroid use or in delayed puberty
- Involve endocrinologist in starting therapy & follow-up endocrine care

# Thyroid Controversy

- use of TSH >3mU/L as diagnostic criterion for mild hypothyroidism
- upper limit of TSH in healthy adults
- in adults, treatment not usually started unless TSH is persistently >10mU/L
- mild TSH elevation provides opportunity to treat a short child
- Based on the thyroid treatment study, short children with FA & borderline TFT's may benefit from thyroid hormone therapy.

- use of GH therapy in FA
- increased risk of malignancy
  - oral pharyngeal & gynecological cancers
  - risk of developing acute myelogenous leukemia (AML)
- unknown whether GH therapy could increase these risks

# Childhood cancer survivors

- new leukemia in GH-treated patients without risk factors
  - not different from that of general population
- limited data
  - GH-treated FA subjects are not at higher risk of AML (or other malignancies) than are FA subjects not treated with GH
- A short child with FA should be treated with GH
  - after HCT
  - if has GHD
  - not just for short stature or SGA
  - Controversial:
    - use of GH prior to HCT, or in absence of GHD

# GH patient registries

- useful safety & efficacy data re: use of GH in general population
- few subjects with FA
- Many adults with FA have had nasopharyngeal cancer or cervical cancer
  - lifelong cancer risk even if bone marrow has been corrected by HCT
- experience with GH use in FA is too small for definitive conclusions

# Insulin therapy

- Blood sugars should be checked 2H after start of meal
  - initially after each meal
  - eventually not necessary
- If blood sugar after eating remains >180mg/dL
  - increase insulin to 1 unit for 25g
  - then 1 unit for 20g, and so on
- Ideal treatment goal
  - post-prandial glucose of 90 to 150mg/dL without hypoglycemia

# Delay in a girl

- In FA girls expected to reach adequate adult height
  - slowly increase estrogen dose every 6mo until full replacement of 1.25mg daily
  - when spotting occurs, Provera 10mg by mouth daily for 10 days
- When acceptable adult height is achieved, birth control pills can be used for replacement

# Alternative therapy (delay in boy)

- topical testosterone gel
  - initial dose 1.25mg daily
  - titrate to achieve reasonable serum levels for age & height
  - Initial goal might be testosterone of 50ng/dL
- Low dose testosterone dosing
  - Maintain several years while boy grows taller
  - rapid increase in testosterone dose should be avoided
- When acceptable adult height is achieved, adult testosterone dosing can be used for replacement

# Bisphosphonates

- More aggressive intervention if BMD is low for height with fractures
  - Oral weekly or monthly in adult
  - If ≥2 low impact fractures
  - If DXA result < -1.5 SD (after adjustment for height age)
- Treat any hormone deficiency, especially treat for pubertal delay

- Oxidative repair mechanism is implicated in etiology of deficiencies
- Persons with FA now have significantly extended lifespan
- We need to address quality of life issues, such as adult height