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

- **Hormones**
  - made in one part of body
  - carried in the blood
  - carry message to another part of body

- **They control**
  - childhood growth
  - energy & stamina
  - blood sugar
  - bone mineral
  - sexuality & fertility
CCHMC FA endocrine database

I will present data from 120 persons with FA enrolled in my database.

<table>
<thead>
<tr>
<th></th>
<th>Growing</th>
<th>Adult height</th>
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<tr>
<td>number</td>
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<td>42</td>
</tr>
<tr>
<td>female</td>
<td>43</td>
<td>19</td>
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<tr>
<td>age range</td>
<td>0.3-15.9y</td>
<td>13.5-31y</td>
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<tr>
<td>after HCT</td>
<td>22%</td>
<td>51%</td>
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<tr>
<td>FA type--FANCA</td>
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<td>31</td>
</tr>
<tr>
<td>FA type--other</td>
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Outline of talk

• Hormones by age
  – Weight
  – Glucose & insulin
  – Growth/ Height
  – Hypothyroidism
  – Growth hormone deficiency
  – Puberty/ Gonadal function
  – Bone mineral

• Evaluation

• Therapy
Weight

- Often below average

- Body mass index (weight adjusted for height)
  - Children -0.2 SD (zero is average)
  - Adults -1.0 SD

- Low weight for height ("failure to thrive")
  - Children 33%
  - Adults 38%

- Overweight for height
  - Children 11%
  - Adults 2%
Body Mass Index, CCHMC (in SD units compared to average)
Factors affecting weight

• small appetite
• malabsorption
• increased calorie needs during illness
• low insulin secretion
  – insulin deficiency leads to poor weight gain
  – blood sugar rises, lose glucose in urine
Glucose-insulin control

• The body’s ability to use nutrition
  – Depends on insulin secretion
  – Insulin influences growth & health

• After intake of meal
  – There is a rise in glucose, then rise in insulin

• Normally, glucose does not change much
Impaired insulin secretion (Elder 2008)

- Findings on oral glucose tolerance test
- In 39 children with FA
  - 8% -- diabetic
  - 46% -- impaired glucose tolerance
  - Insulin
    - fasting levels low
    - initial insulin rise sluggish
    - later high insulin after glucose in 72%
  - consistent with beta cell dysfunction
Glucose after oral glucose load (OGTT)

OGTT Glucose

Glucose area under curve

AGM, abnl glucose metabolism; NGT, normal glucose tolerance; REF, reference group

Elder 2008
Insulin after OGGT

OGTT Insulin

Insulin area under curve

AGM, abnl glucose metabolism; NGT, normal glucose tolerance; REF, reference group

Elder 2008
Postprandial glucose & insulin, CCHMC
**Glucose/ Insulin**

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

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• **Evaluation**

• **Therapy**
Height, CCHMC

- Parents’ heights normal
- 48% had low weight at birth
  - can affect later growth
- Height not affected by transplant
- 60% were shorter than 3rd %ile
  - for general population
Height, CCHMC adults

- **Women**, 152 cm (5 ft), -1.8 SD
  - Range
    - 4 ft 6 in – 5 ft 5 in
    - 137 - 167 cm
- **Men**, 160 cm (5 ft 3 in) -2.3 SD
  - Range
    - 4 ft 9 in - 5 ft 10 in
    - 145 – 179 cm
Height, CCHMC (in SD units below average)
Outline of talk

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- **Evaluation**

- **Therapy**
Hypothyroidism

- Thyroid hormone levels are often mildly abnormal in FA
  - borderline low T4 or FT4
  - borderline high TSH (values >3 are suspicious)
Low thyroid function, CCHMC
Thyroid Study (Eyal 2008)

- Placebo-controlled trial of thyroid therapy
  - supported by FA Research Fund
- 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 was faster on thyroid hormone than on placebo
- Conclusion:
  - If FA children have borderline TFT’s, T4 therapy may improve their growth
Growth Velocity (GV) during placebo & thyroid therapy (8 children with FA)

Eyal 2008
GH Deficiency (GHD)

- Only a rare patient with FA has GHD
  - 12% have low GH peak
  - But sometimes not short, or growing OK
- Among adults with FA
  - GH & cortisol are not different from general population
  - Not different by transplant status or by gender
Outline of talk

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• **Evaluation**

• **Therapy**
Pubertal timing

• 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.
Gonadal function in FA

- Infertility in some men with FA
- Early menopause in some women with FA
- Related to FA itself or to transplant
- If testosterone or estradiol are low
  – lower sex drive or low bone mineral
Gonadal function, CCHMC adults

- High LH & FSH is seen in gonadal failure
  - LH was high in 25%
    - After transplant
      - 43% of men
      - 17% of women
  - FSH was high in 43%
    - After transplant
      - 62% of men
      - 17% of women
Gonadal function, CCHMC

![Graph showing gonadal function with Luteinizing hormone and Follicle-stimulating hormone axes.]
Bone mineral development

• Controlled by
  – Nutrition
  – Exercise
  – Vitamin D, calcium
  – Growth hormone
  – Gonadal hormones
Bone mineral by age

Peak BMD at about age 25y, then gradual decline
Bone Mineral Density (BMD)

- BMD in FA (articles prior to ours)
  - in children after transplant
    - BMD declined in 1st 6 months
  - in 13 adults
    - osteopenia or osteoporosis compared to normal for gender & age

- Dual photon X-ray absorptiometry (DXA)
  - overestimates osteopenia in small stature
    - If scan through a smaller bone, lower total mineral
  - Need to adjust for height age
BMD, CCHMC adults

- BMD averages -0.8 SD
  - However, if DXA result is adjusted for height, BMD is often normal
- Low BMD adjusted for height
  - Children 3%
  - Adults 13%
- Not significantly lower after transplant
Bone Mineral Density by age, CCHMC
Bone Mineral Density by height SD, CCHMC
BMD in FA (Rose 2011)

- Our findings in children
  - BMD in FA is normal
    - if DXA result is adjusted for height age
      - regardless of whether they had transplant

- We recommend
  - Encourage adequate vitamin D & calcium intake
  - Do DXA if after transplant or if hypogonadal
Outline of talk

• Endocrine function
• Evaluation
• Therapy
Annual evaluation

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

- adequate calories & regular exercise
- sufficient calcium & vitamin D
- avoid concentrated sweets
  - complex carbohydrates
  - instead of simple sugars
Insulin

• If hyperglycemia
  – post-prandial glucose > 180mg/dL
    • Check blood sugars 2H after start of meal
  – Use short-acting insulin at meals
    • “cover” for carbs

• Long-acting basal insulin
  – not needed if fasting glucose is normal
Thyroid hormone

- Use 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

• **In short girl** without puberty
  – Use **low dose** estrogen
  – Avoid rapid increase in estrogen dose

• **In woman** without menstrual periods
  – Use standard low dose estrogen/progesterone (pill, patch)
Testosterone

• **In short boy without puberty**
  – Use **low dose** testosterone (shot, gel)
  – Observe for pubertal progression for next 6m

• **In man**
  – Use testosterone injections im every 2 weeks or testosterone gel applied to skin
Bone therapy

• Adequate dietary calcium & vitamin D

• Elemental calcium:
  – 800mg daily in young child
  – 1000 to 1500mg in adolescent
  – 1200mg in adult

• Vitamin D:
  – 1000 to 1500 units daily

• Bisphosphonates
  – if BMD low with fractures
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