

Endocrine issues in FA

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- ▶ 80% of children and adults with FA have an endocrine abnormality
- ▶ Endocrine cells make a hormone (message)
 - ▶ Carried in bloodstream to other cells
 - ▶ Hormone messages tell body to grow, or go through puberty...
- ▶ Cause of low hormone
 - ▶ unrepaired DNA damage from oxidative injury
 - ▶ loss of endocrine cells, so lower hormone level

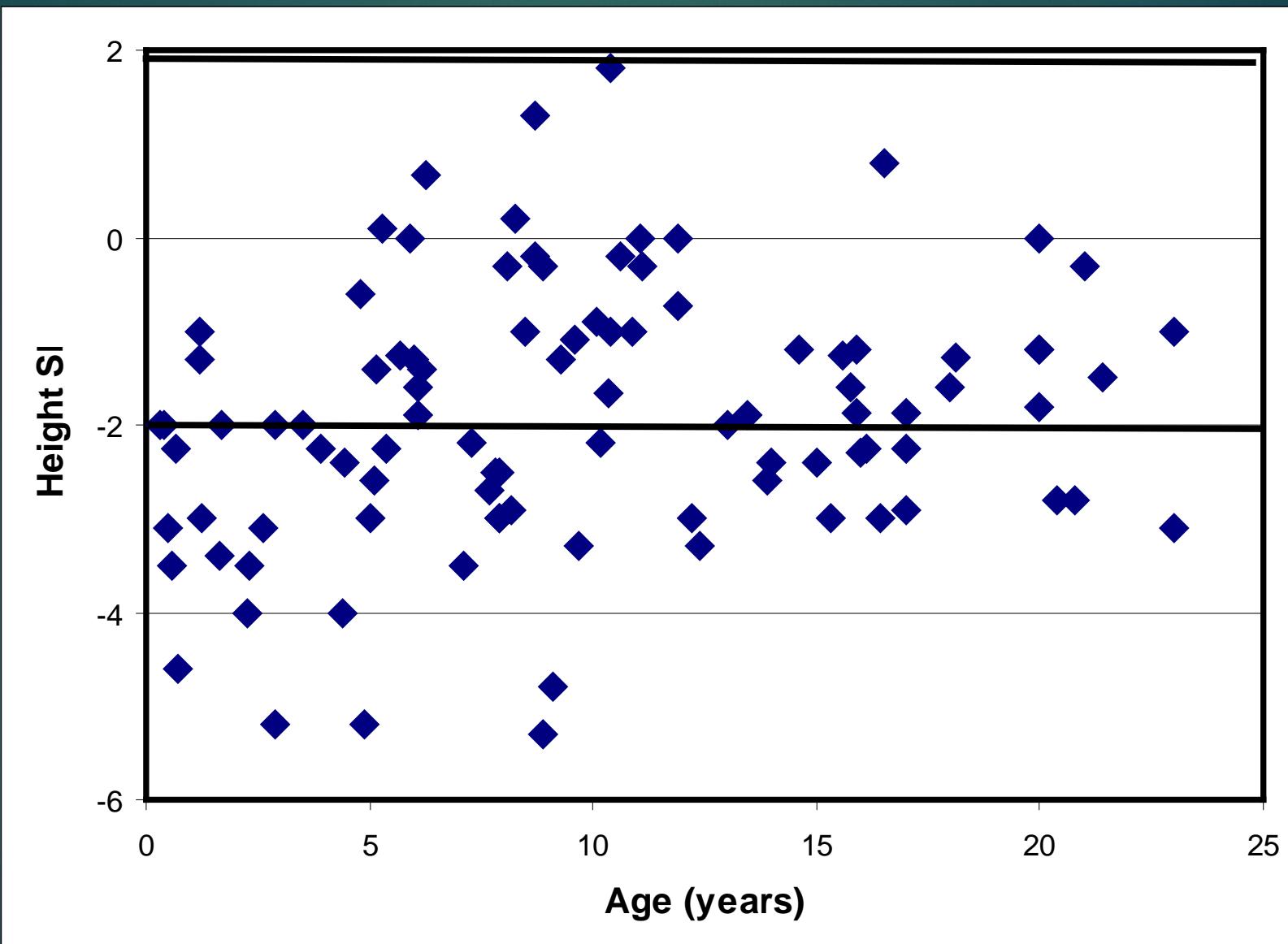
Outline

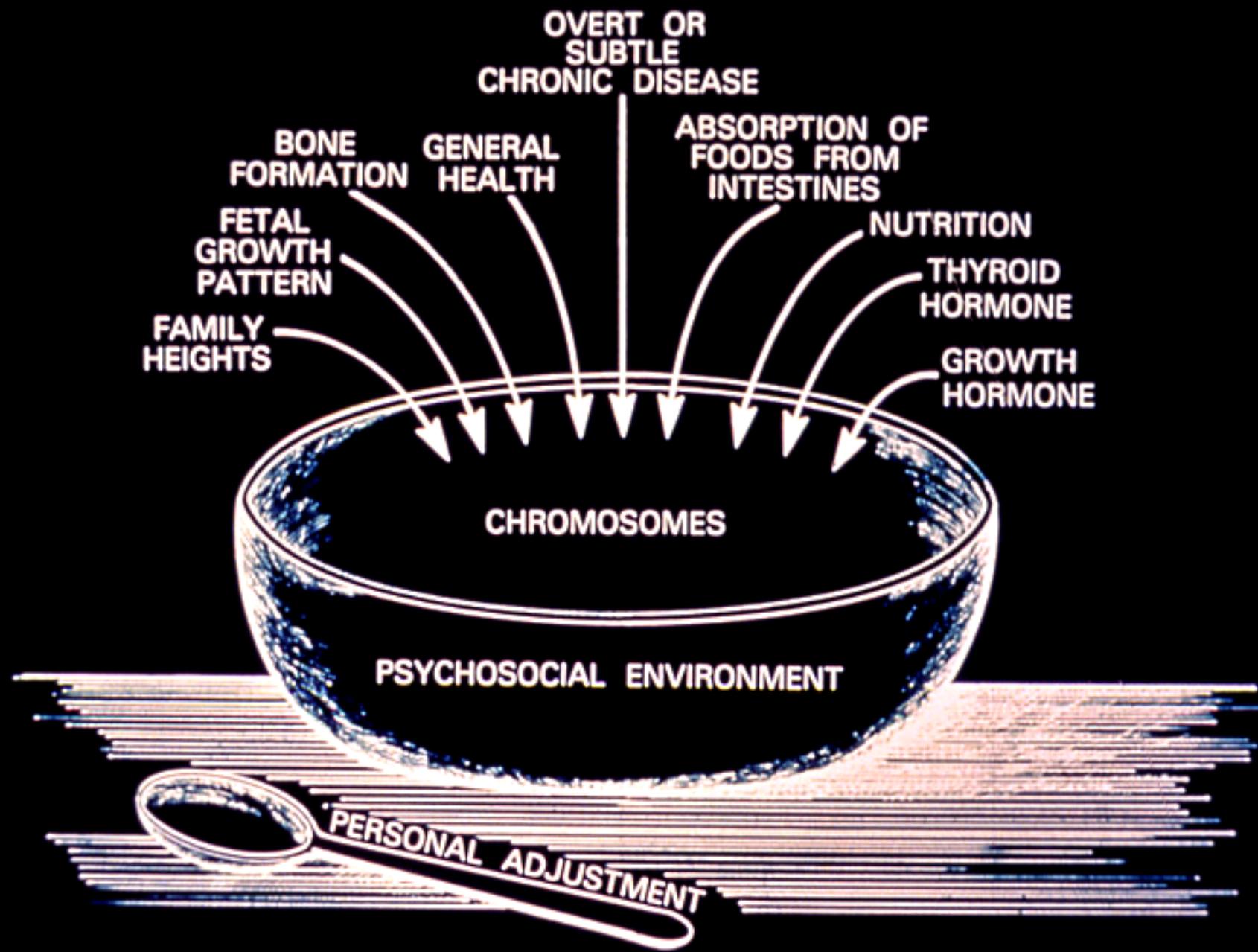
- ▶ Endocrine issues in FA include
 - ▶ Short stature
 - ▶ Hypothyroidism
 - ▶ Growth hormone (GH) deficiency
 - ▶ Abnormal glucose with low insulin secretion
 - ▶ Early or late puberty, irregular periods, infertility
 - ▶ Low bone mineral

Short stature

- ▶ Lower height than expected for parents' heights
- ▶ Shorter than average, only about half are within normal range
- ▶ Average adult height
 - ▶ men 160 cm, 5 feet 3 inches
 - ▶ women 150 cm, 4 feet 11 inches
- ▶ Important to identify underlying cause in order to treat
 - ▶ endocrine -low thyroid hormone, low GH, late puberty
 - ▶ non-endocrine --undernutrition, vitamin D deficiency, FA mutation, small for gestational age at birth (SGA), transplant medications
- ▶ Healthy nutrition is important in order to have optimal growth

Height (in SD units below average)





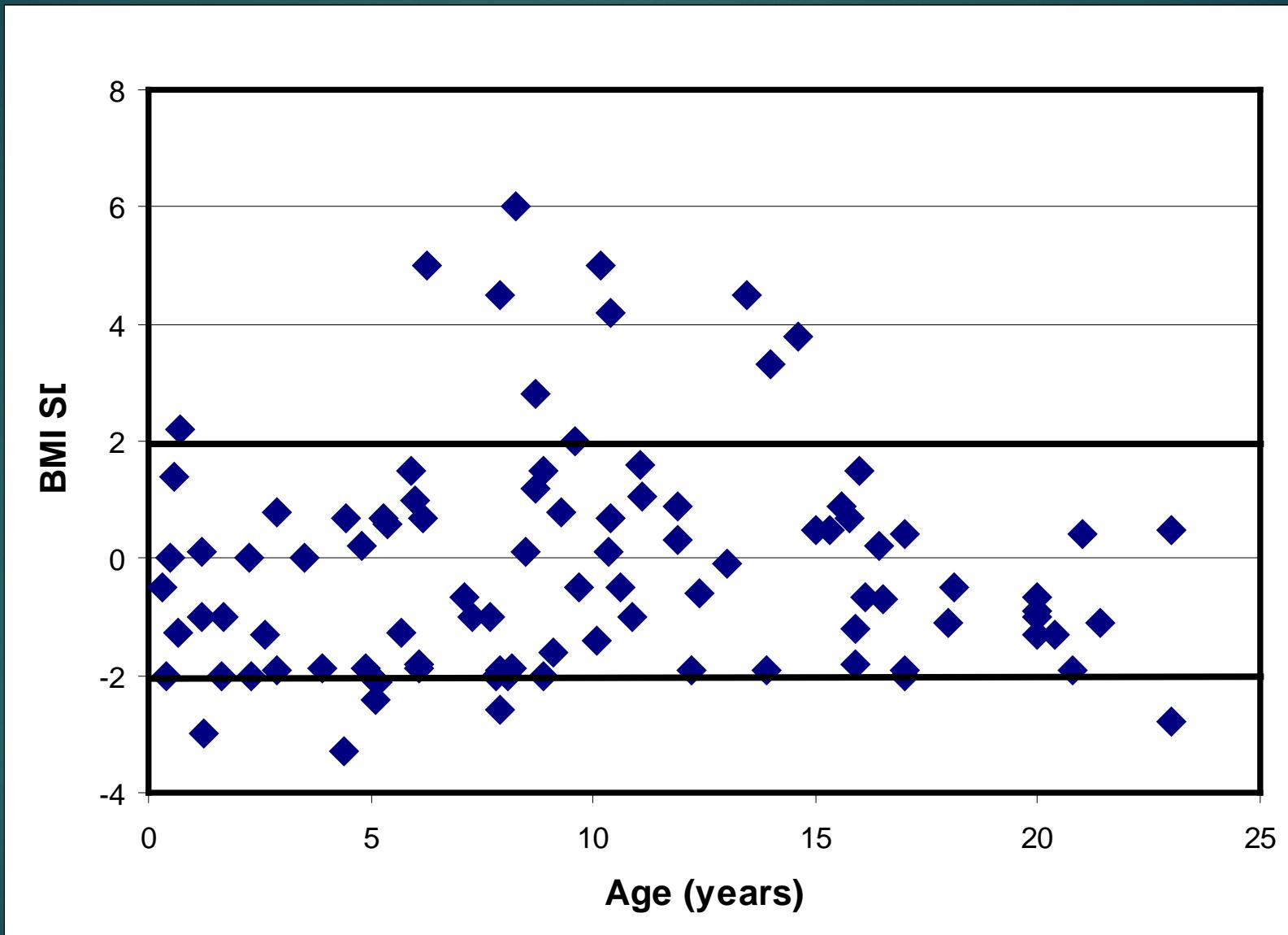
Growth Screening

- ▶ Yearly height and weight
- ▶ Identify and treat nutritional and other medical causes for poor growth as early as possible
- ▶ Assess thyroid & growth hormone, & pubertal status
- ▶ Treat any deficiency of thyroid hormone, vitamin D, GH, or pubertal hormone

Undernutrition/ lipids/ obesity

- ▶ Screening
 - ▶ Yearly weight & BP
 - ▶ Fasting lipid profile yearly in patients >10 years
 - ▶ Nutritional intake should be assessed by registered dietician
- ▶ Treatment
 - ▶ Include sufficient calories, protein, calcium, and vitamin D
 - ▶ Maintain healthy diet and exercise

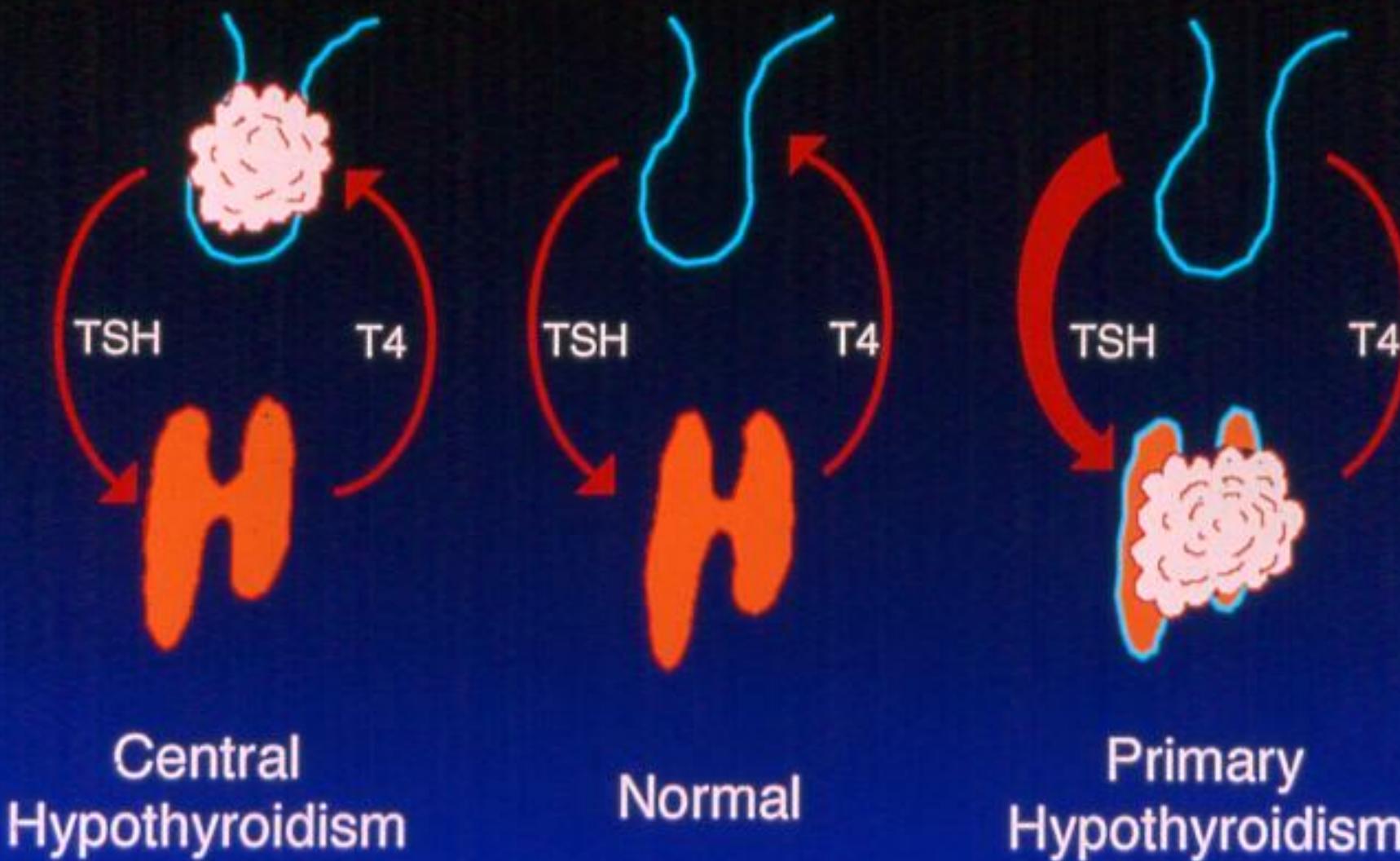
Body Mass Index (in SD units compared to average)



Thyroid hormone

- ▶ TSH is a message from pituitary to thyroid gland
 - ▶ TSH = thyroid-stimulating hormone
- ▶ Then thyroid gland makes thyroxine
 - ▶ T4 = thyroid hormone
- ▶ T4 may be protein-bound in the blood, or may be protein-free
 - ▶ FT4 = free T4

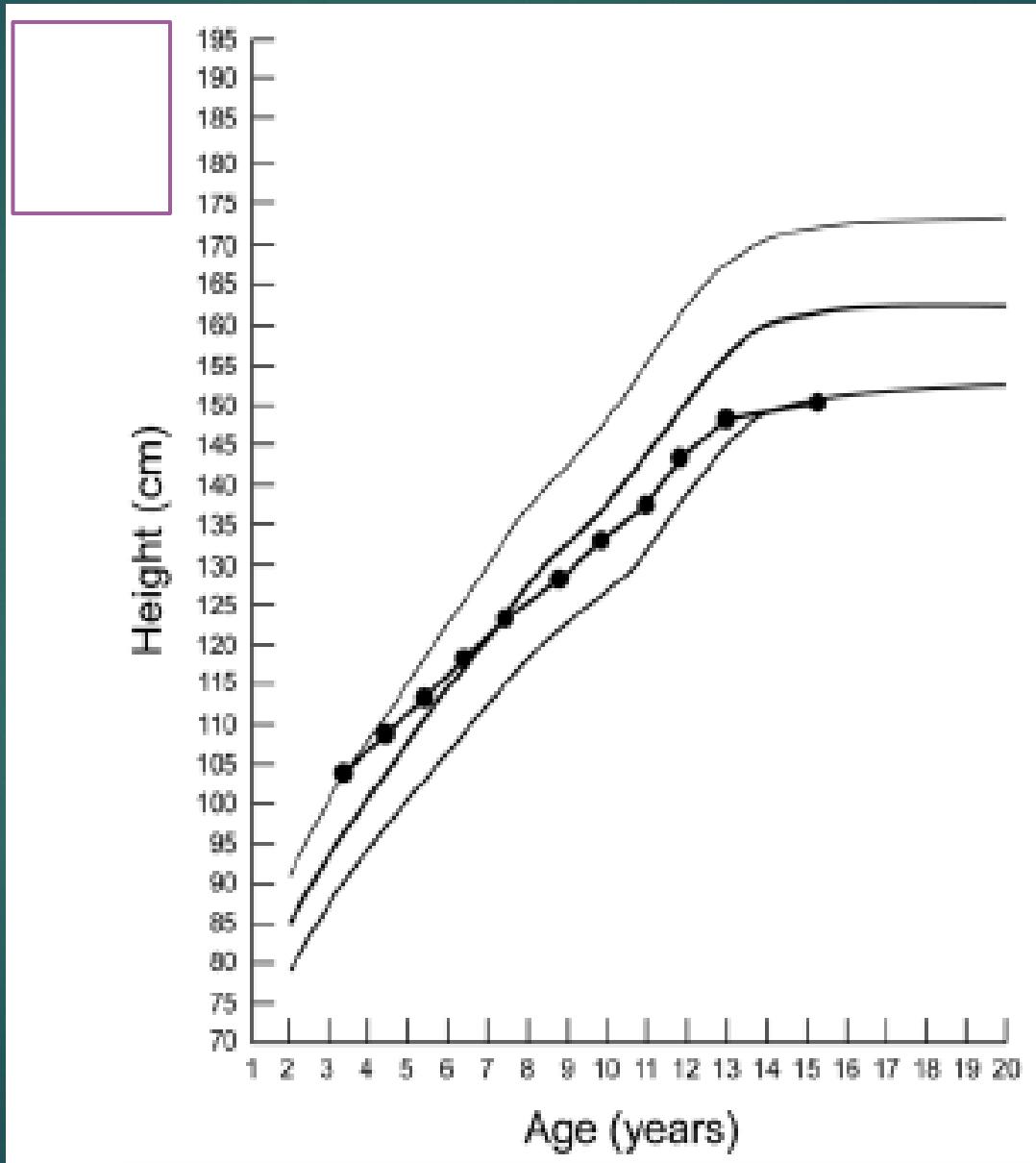
HYPOTHALAMIC-PITUITARY-THYROID AXIS



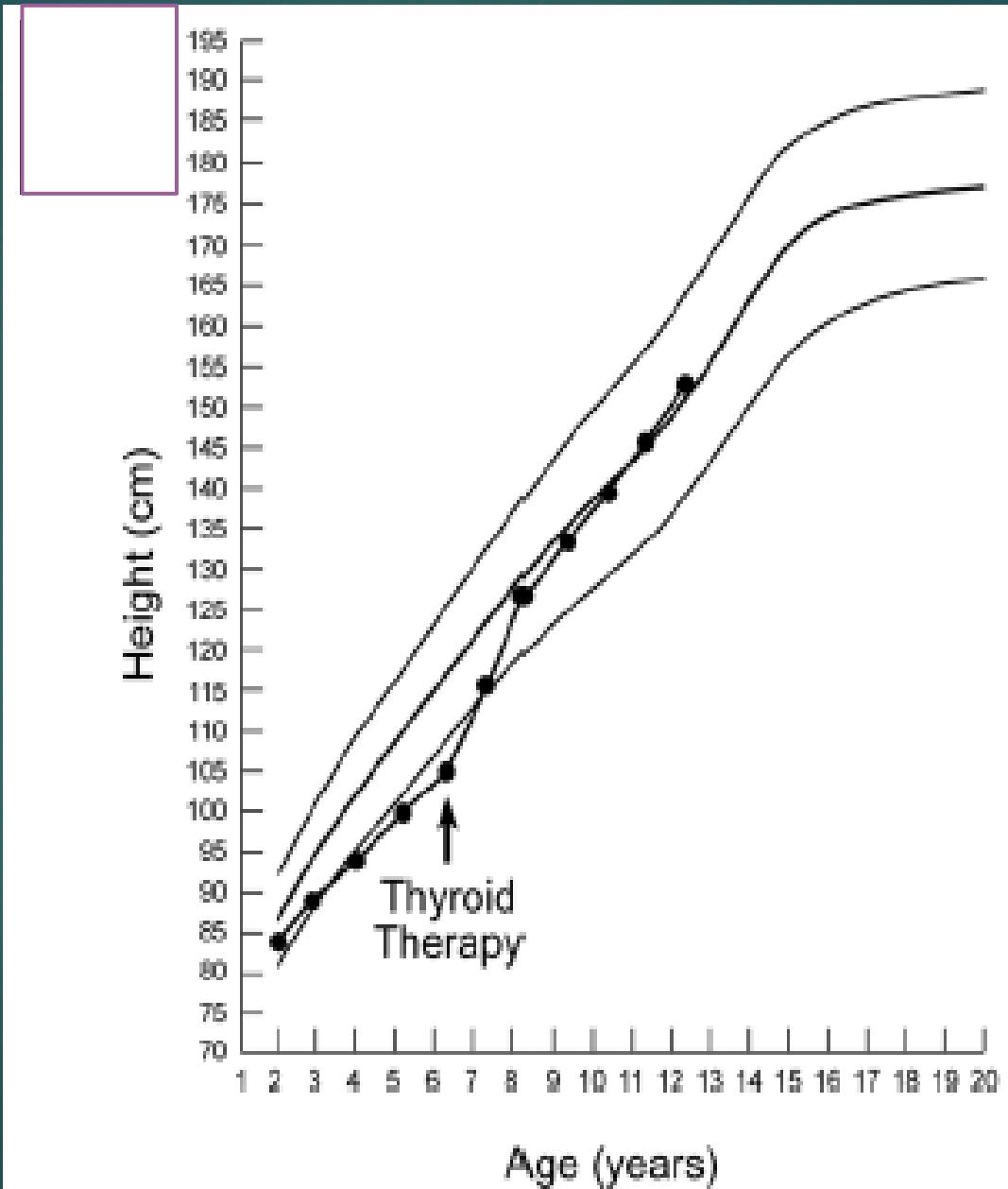
Hypothyroidism

- ▶ If TSH is high, thyroid therapy may increase growth rate
- ▶ Start thyroid therapy if FT4 is low, or TSH is over 3 mU/L
 - ▶ particularly if younger than 3 years of age
- ▶ Target for thyroid dose is
 - ▶ TSH of 0.5 to 2 mU/L in primary hypothyroidism
 - ▶ FT4 just above mid-normal in central hypothyroidism
 - ▶ (TSH will be suppressed)

Hypothyroidism



Thyroid hormone in central hypothyroidism



Thyroid Screening

- ▶ Yearly FT4 & TSH on 8 am blood sample
- ▶ Primary hypothyroidism
 - ▶ TSH over 3 mU/L
- ▶ Central hypothyroidism
 - ▶ low FT4 & ratio of (8am TSH) to (TSH after 10am) of less than 1.3
- ▶ If central hypothyroidism is identified,
 - ▶ also test for ACTH deficiency & pituitary magnetic resonance imaging (MRI)

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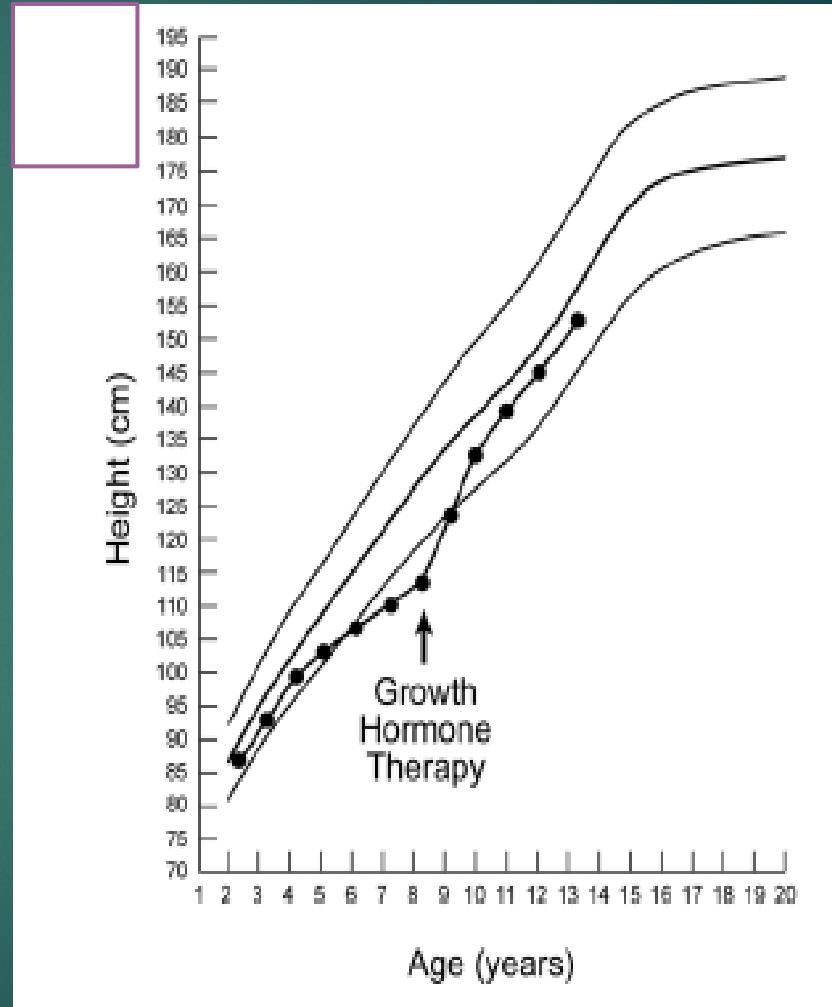
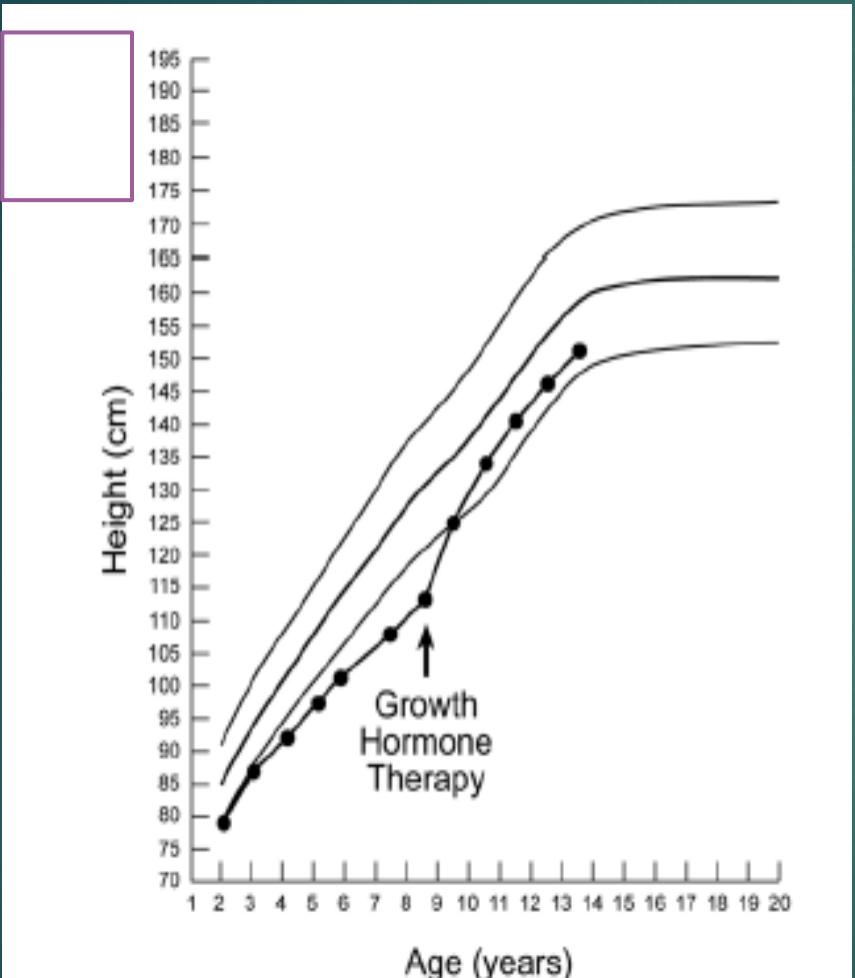
Growth hormone

- ▶ GH is a message made by pituitary
- ▶ GH acts all over body
- ▶ Body cells make IGF-I
 - ▶ IGF-I = insulin-like growth factor
- ▶ IGF-I is carried in bloodstream by IGFBP3
 - ▶ IGFBP3 = IGF-binding protein

Screening for GH deficiency

- ▶ If child is short, growth rate slow, IGF-I & IGFBP3 low
- ▶ Evaluate GH
 - ▶ 2 GH stimulation tests (clonidine, arginine, or glucagon)
- ▶ GH is normal if
 - ▶ it rises to 10 ng/mL or greater on any test
- ▶ If GHD is identified
 - ▶ also test for central hypothyroidism, ACTH deficiency, and MRI scan of brain & pituitary

GH therapy in GH deficiency



Treatment of GHD in FA

- ▶ GH deficiency --treat with GH therapy
- ▶ Counsel family about
 - ▶ predicted adult heights
 - ▶ effects of GH therapy on growth rate
 - ▶ potential risks and benefits of GH treatment
- ▶ Titrate GH dose to achieve IGF-I in mid-normal range for age (between 0 and +1 SD)
- ▶ Stop GH therapy if bone marrow clone develops
- ▶ There is no consensus on safety of GH therapy in FA
 - ▶ continue to be concerns about long term safety after GH therapy, even in children with normal medical history

Pituitary hormone deficiencies

- ▶ Includes GH, TSH, LH & FSH (ovary/ teste function)
- ▶ Also ACTH is needed to make cortisol in adrenal glands
 - ▶ ACTH = adrenocorticotrophic hormone
 - ▶ Cortisol = message needed during illness
- ▶ Test for ACTH insufficiency if other pituitary hormone deficiencies are present

Pituitary Screening

- ▶ Obtain MRI of brain & pituitary in any FA patient with
 - ▶ growth failure, height below 5th %ile, or any pituitary hormone deficiency
 - ▶ often pituitary is smaller with thinner stalk than in age-matched children without FA
 - ▶ may show PSIS (pituitary stalk interruption syndrome)

Glucose and insulin

- ▶ Insulin is made in pancreas (near the stomach)
 - ▶ More is made when you eat
 - ▶ Less is made when going without food
- ▶ Keeps blood sugar in tight glucose range of 60 to 105

Abnormal Glucose or Insulin

- ▶ In FA, often there is high glucose after eating
- ▶ Insulin is not made quickly after eating in FA
- ▶ Steroid therapy or androgens can worsen this

Glucose Screening

- ▶ Yearly testing for glucose & insulin
 - ▶ Fasting glucose & insulin, plus another glucose & insulin 2 hours after a meal (post-prandial)
 - ▶ Getting only fasting glucose may miss identifying impaired glucose tolerance
- ▶ Glycosylated hemoglobin (HbA1c)
 - ▶ Measures amount of glucose attached to hemoglobin in red cells
 - ▶ not helpful prior to HCT
 - ▶ HbA1c may be more useful as a screen after HCT

Treatment of high glucose

- ▶ Low glycemic index diet slows absorption of sugar
 - ▶ Carbohydrate plus protein & fat
- ▶ Avoid concentrated sweets/ sugar (juices, soda, candy)
- ▶ Ensure enough calories & regular exercise
- ▶ During HCT, often there is hyperglycemia related to steroid therapy
 - ▶ Need both long-acting & short-acting insulin
- ▶ If glucose after eating is consistently above 180 mg/dL, use short-acting insulin at meals
- ▶ Can use metformin in overweight teen with FA
 - ▶ potential risk for side effects is not known

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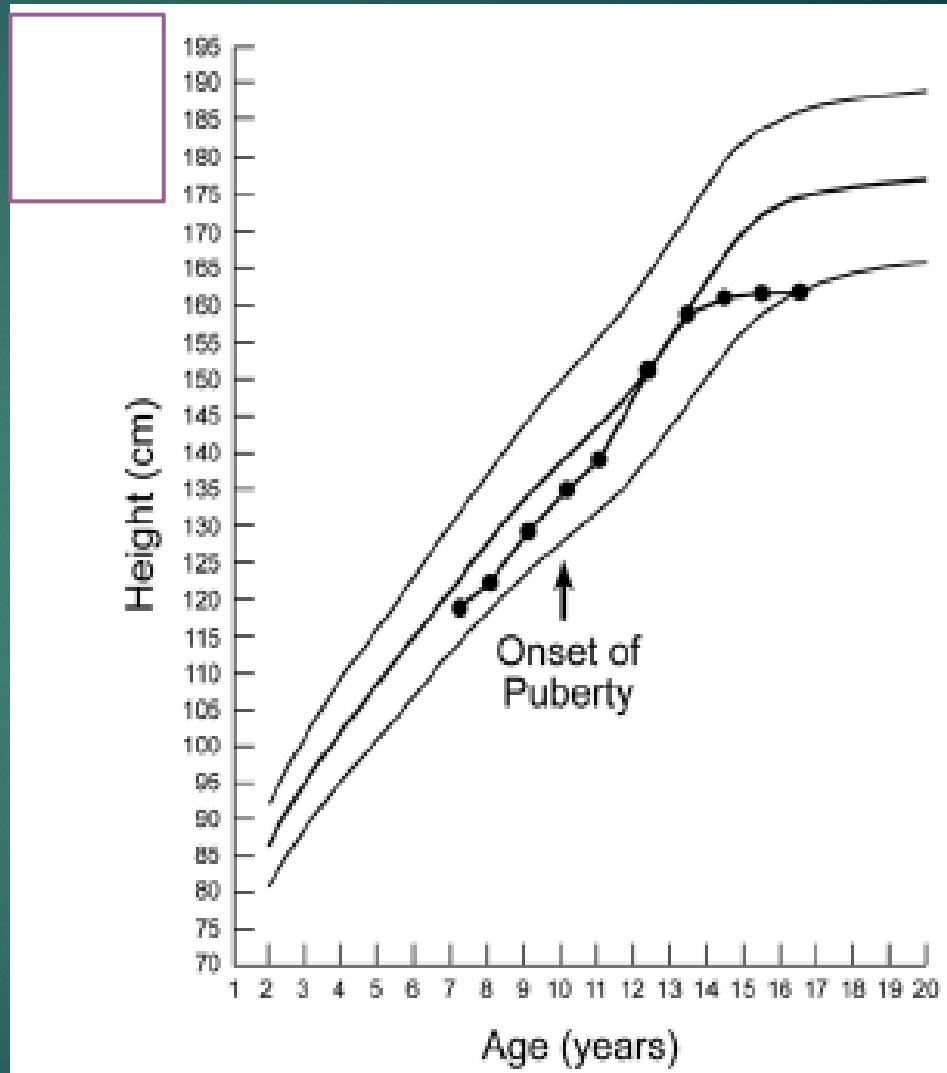
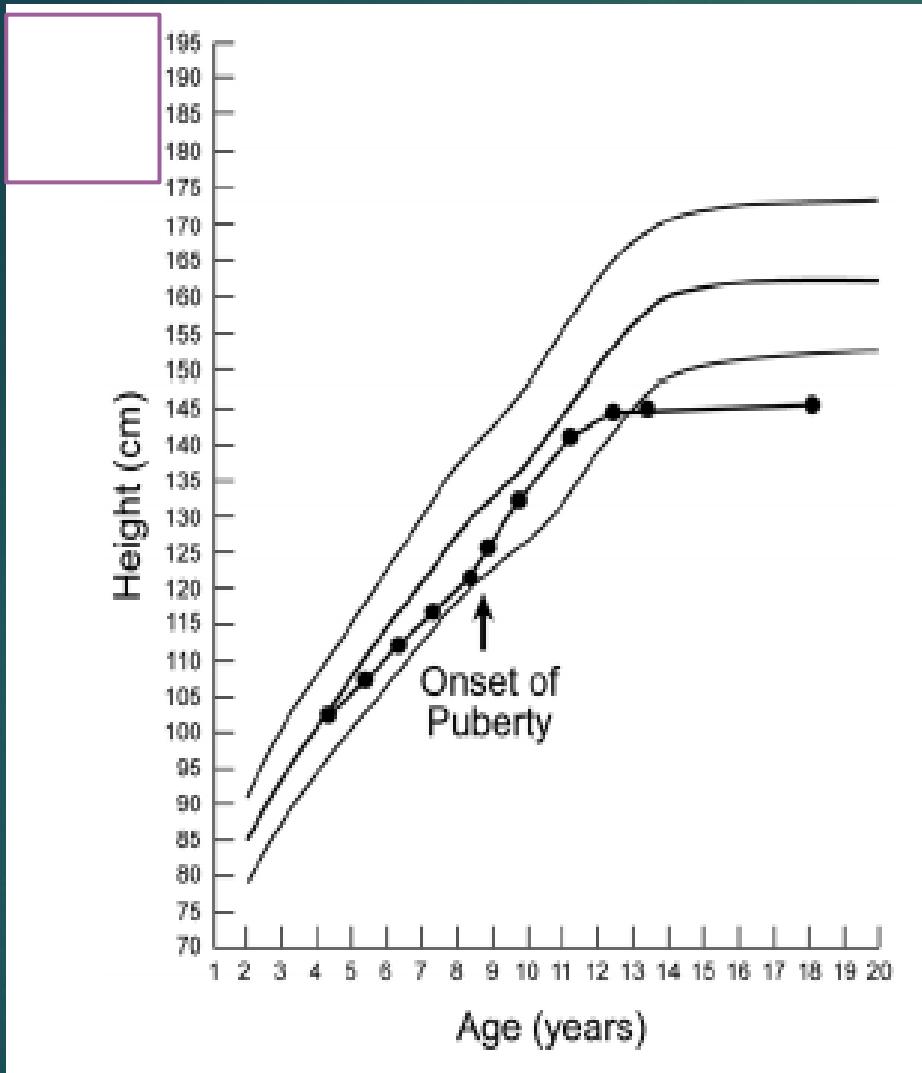
Puberty, hypogonadism, fertility

- ▶ In FA, onset of puberty may be early, normal, or late
- ▶ Early = signs of puberty prior to height age of typical 10y
- ▶ Delay = no signs of puberty
 - ▶ by age 14y in boy, by age 13y in girl
- ▶ Causes of delayed puberty in FA
 - ▶ Chronic illness, poor weight gain, total body irradiation, some chemotherapy agents
 - ▶ GH or thyroid hormone deficiency
 - ▶ Decreased fertility after HCT

Puberty Screening

- ▶ Yearly check: onset of puberty, pubertal stage, rate of puberty, growth
 - ▶ Tanner staging of pubic hair, breast development (in girls), testicular size (in boys)
 - ▶ If early or delayed puberty, obtain bone age
 - ▶ Hormone levels
 - ▶ Girls--LH, FSH, estradiol, & AMH
 - ▶ Boys--LH, FSH, testosterone, & inhibin B

Rapid/early puberty



Treatment of early puberty

- ▶ GnRHa therapy (gonadotropin releasing hormone agonist) to delay puberty
- ▶ Treatment can add 4 to 5 cm to adult height during 4 years of therapy

Treatment of delayed puberty

- ▶ Treat delayed puberty--sex steroid therapy
 - ▶ Take into account height & growth potential
 - ▶ Avoid rapid increase in dose
 - ▶ Start at low dose & increase over several years to adult dose
 - ▶ Treatment increases bone mineralization, optimize growth rate
- ▶ Boys --Testosterone --topical gel or injections
- ▶ Girls --Estrogen therapy—patch or oral
 - ▶ Progesterone --add 3 monthly when spotting occurs, or after 2 years

Bone mineral density

- ▶ Risk for low BMD with fractures
 - ▶ Prolonged or high dose corticosteroids
 - ▶ Immobility
 - ▶ Hypogonadism
 - ▶ GH deficiency

Bone Screening

- ▶ Yearly check on 25OH vitamin D level, history of dietary intake of vitamin D & calcium
- ▶ Assess bone mineral density (BMD)
 - ▶ By dual energy absorptiometry (DXA)
 - ▶ Before HCT & one year after HCT
 - ▶ At about age 14 years if there has been no HCT
 - ▶ Adjust for height age
 - ▶ <http://www.bmdcspublic.com/zscore.htm> to calculate height-adjusted Z-score

Bone Treatment

- ▶ If vitamin D is below 30 ng/mL, treat with vitamin D
- ▶ Adequate dietary intake
 - ▶ Calcium (800 -1000 mg elemental daily)
 - ▶ Vitamin D (800 -1000 units daily)
- ▶ Bisphosphonate therapy if
 - ▶ Height-adjusted BMD Z-score lower than -2.0 SD
 - ▶ Plus fractures (long bone fracture of leg, vertebral compression fracture, or 2+ long bone fractures of arm)

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

