Pediatric Growth Disorders and Growth Hormone
Pediatric Growth Disorders and Growth Hormone

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Department of Pediatrics
Learning Objectives
At the end of this lecture, participants will be able to:

1. Discuss phases of normal growth for pediatric patients

2. Recognize, evaluate and treat the following conditions in children
   - Constitutional growth delay
   - Idiopathic short stature
   - Chronic malnutrition with stunting of growth
   - Growth hormone deficiency
   - Small for gestational age
   - Turner Syndrome
Intrauterine growth
- occurs at a rate approximately 1.2 to 1.5 cm per week
- Peaking at midgestation (18 weeks) 2.5 cm per week
- Slowing to 0.5 cm just before birth

Birth to 2 years
- After birth rate of growth is most rapid-Peaking at 25 cm per year
- The average length at birth for a term infant is 20 inches (50 cm)
- Infants grow 10 inches (25 cm) during the first year of life
- grow 4 inches (10 cm) between 12 and 24 months

Toddlers
- 3 inches (7.5 cm) between 24 and 36 months
- 3 inches (7.5 cm) between 36 and 48 months
- reach one-half of their adult height by 24 to 30 months

Phases of Normal Growth

- **Children**
  - grow 2 inches/year (5 cm/year) between age four years and puberty
  - normal deceleration of height velocity before the pubertal growth spurt

- **Puberty**
  - **Girls**
    - Average age of pubertal growth spurt 10.5 years of age
    - Peak height velocity
      - during early puberty (Tanner stages II to III)
      - 6 to 10 cm/year
  - **Boys**
    - Average age of pubertal growth spurt 12.5 years
    - Peak height velocity
      - During mid-puberty (Tanner stages III to IV)
      - 5 to 11 cm/year


Weight gain

- First few days of life
  - may lose up to 10 percent of their birth weight

- By 10 to 14 days
  - Typically regain their birth weight

- Until three months of age
  - gain approximately 30 g/day (1 oz/day)

- Three and six months of age
  - gain approximately 20 g/day (0.67 oz/day)

- 6 and 12 months of age
  - 10 g/day

- Double their birth weight by four months of age

- Triple their birth weight by one year of age

- Children gain 2 kg/year (4.4 lbs/year) between two years and puberty

- A prepubertal child whose weight velocity is <1 kg/year (<2.2 lbs/year) should be monitored closely for progressive nutritional deficits

• Child should be fully erect
• head in the Frankfurt plane
• Areas that should touch vertical axis of the stadiometer
  – back of the head
  – thoracic spine
  – buttocks
  – heels
• heels should be together.
• serial measurements should be made at the same time of day
• standing height may undergo diurnal variation.
• should be performed by a trained individual
• heights should be measured in triplicate
• variation should be no more than 0.3 cm
• mean height should be recorded.
• This is your first visit with Tina A. Small.
• She is a healthy 30 month old girl who was referred for evaluation of short stature.
• Mother is 4’11 and father is 5’6

*What is your differential diagnosis for short stature*
Differential Diagnosis for Short Stature

Normal Variants of Growth
- Familial short stature
- Constitutional growth delay
- Small for Gestational age

Endocrine causes of growth failure
- Hypothyroidism
- Cushing Syndrome
- Growth Hormone Deficiency

Genetic Diseases associated with poor growth
- Prader Willi Syndrome
- Turner Syndrome
- SHOX mutations
- Noonans syndrome

Systemic Disorders effecting growth
- Undernutrition
- Glucocorticoid therapy
- Gastrointestinal disease
  - Celiac disease
  - Crohns disease
- Rheumatologic disease
- Renal disease
- Cancer
- Pulmonary disease

Skeletal Dysplasia
- Achondroplasia
- Osteogenesis Imperfecta
- Hypochondroplaisa
• Mother 4’11(59 in) & Father 5’6 (66 in)
• MPH:In: (Father’s Height - 5 + Mother’s Height) / 2
  (66 in - 5 + 59 in)/2 = 60 in

• During early infancy, height and weight both simultaneously decelerate, then stabilizes paralleling the normal growth curve

• Normal growth velocity
• Normal weight for length
• Normal bone age
• Child’s height percentage consistent with midparental height percentile

• What is your diagnosis?
  • Familial (genetic) short stature
Case #2

- This is your visit with Tina C. Small
- She is a healthy 30 month old girl who was referred for evaluation of short stature.
- Mother had menarche at age 11. Father stopped growing after high school
- Tina C. Small returns at age 13 year for poor growth
- She just developed breasts (tanner II). She has no acne, no axillary hair, no pubic hair, and no menses
What is the average age for pubertal development for females?

- Breast buds tanner stage II
  - Avg. 10.9 years

- Growth acceleration
  - peak prior to menarche)
  - Avg. 12 years

- Menarche
  - usually 1½–2 years after onset of puberty
  - Avg. 12.7 years

So Tina’s pubertal development is delayed
Growth Chart at 30 months of age

• During early infancy height and weight both simultaneously decelerate

• Then stabilizes paralleling the normal growth curve
Growth Chart at 13 years of age

- Normal growth rate
- Normal to low normal BMI

What is your diagnosis?

Constitutional growth delay
• Diagnosis of exclusion

• Healthy short children with no identified etiology for poor growth
  – No systemic illness
  – No endocrine disorders
  – No genetic syndromes
  – No bone dysplasias
  – No SGA

By definition these children are > 2.25 SD below the mean in height and are unlikely to catch up in height
  – <63 inches for boys
  – < 59 inches for girls

• Comprise nearly 80% of the short children who present to a pediatric clinic
• The mean increase in adult height in children with ISS with growth hormone therapy (average duration 4-7 yr) is 1.5-3 inches\(^1\-^2\)

• Combined therapy with GnRH analog plus growth hormone in central precocious puberty.
  – 7.9 +/- 1.1 cm in patients treated with GH combined with GnRH analogue
  – Patients treated with GnRH analogue alone the gain was just 1.6 cm +/- 1.2 (p=0.001)\(^3\)

• Aromatase inhibitors
  – Reduce conversion of androgens to estrogen
  – Limit estrogen induced growth plate closure
  – Randomized, placebo-controlled, multicenter trial reports of 4-6 cm gain in near final height when used with growth hormone\(^4\)

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Wit JM et al. Pediatr Res, (53), 154, 2003\(^1\)
Wilson et al. J Pediatri (43) 415-21, 2003\(^2\)
Pucarelli et al. JPEM, (1), 811-20, 2000\(^3\)
Mauras et al. JCEM, 93(3):823-31,2008\(^4\)
Effect of Growth Hormone Treatment on Adult Height in Peripubertal Children with Idiopathic Short Stature: A Randomized, Double-Blind, Placebo-Controlled Trial


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DOI: http://dx.doi.org/10.1210/jc.2003-031457
Received: August 27, 2003
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First Published Online: July 02, 2013
Effect of Growth Hormone Treatment on Adult Height in Peripubertal Children with Idiopathic Short Stature: A Randomized, Double-Blind, Placebo-Controlled Trial

- Randomized double blind placebo controlled study
- N-68; 53 male and 15 females
- Idiopathic short stature (height or predicted height < -2.5 SD score)
- GH 0.074 mg/kg) or placebo sq three times per week until near adult height
- At study termination adult height available 33 patients
- Mean duration of treatment 4.4 years
- Adult height was greater in GH-treated group than in the placebo-treated group by 0.51 SDS (3.7 cm; P < 0.02; 95% confidence interval
Leschek et al. JCEM, 89(7) 3140-3148, 2004
• This is your first visit with Tina B. Small.
• She is a 30 month old girl who was referred for evaluation of short stature.
• She has a poor appetite and is a picky eater.
• Mother is 5’4” and father is 5’10”.
• Work up reveals delayed bone age
• First weight decelerates, then height decelerates

• Decreased weight for length

• Low BMI

• What is your diagnosis?
  *Chronic malnutrition with stunting of growth*
Malnutrition is considered a leading cause of growth attenuation in children  
Spontaneous catch up growth usually occurs once food is replenished  
Children with marasmus and kwashiorkor have significantly lower height than healthy subjects  
Children with eating disorders from developed countries were on average shorter than controls  

**Good nutrition ensures proper “building blocks” for growth**

Epiphyseal growth plate of male Sprague Dawley rat (34 days old) stained with hematoxylin/eosine/Alcian Blue. Magnification, 100×. The different zones of the growth plate are marked.

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Gat-Yablonski, Nutrients (7), 517-551, 2015
Kilic et al. Clin Biochem, (37), 382-387
Twenty-four-day-old male SD rats were allowed to eat
- AL-ad libitum
- RES- subjected to 40% food restriction for 11 days
- CU- subjected to 10 days of food restriction followed by one day of re-feeding

Food restricted rats gained 1.2 g/day
Ad lib rats 6.5 g/day
When food restriction removed rats had largest increase (15.1 g) on the first day
Bone length increased seven days later

Effect of food restriction and re-feeding on the height of the EGP.

Even-Zohar. *Bone* (42), 505-515, 2008
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Affected by food restriction</th>
<th>Effect on Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Reduced</td>
<td>Stimulates growth</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Increased</td>
<td>Stimulates growth</td>
</tr>
<tr>
<td>Insulin like growth factor</td>
<td>Reduced</td>
<td>Stimulates growth</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Reduced</td>
<td>Inhibits growth</td>
</tr>
<tr>
<td>Leptin</td>
<td>Reduced</td>
<td>Stimulates growth</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>Reduced</td>
<td>Stimulates growth</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>Reduced</td>
<td>Stimulates growth</td>
</tr>
</tbody>
</table>
This is your first visit with Tina D. Small.
She is a 30 month old girl who was referred for evaluation of short stature.
Her parents note that she has not been growing.
Mother is 5’5” and father is 5’9”
She brings an outside bone age which is delayed
Case 4

Simultaneous deceleration of both height and weight

Normal or increased weight for length

Low growth velocity
Case # 4 continued

What is your differential diagnosis?
Growth hormone deficiency, acquired hypothyroidism, or occult disease

What work up do you recommend?
basic metabolic panel, complete blood count, TSH, T4, insulin like growth factor 1, insulin like growth factor binding protein 3, sedimentation rate, tissue transglutaminase IgA

All normal except low IGF 1 and IGF BP3, patient also fails formal growth hormone testing

Diagnosis growth hormone deficiency
1956
- First human to receive GH therapy of bovine origin
- Given for 3 weeks for metabolic balance studies revealing no effects

1958
- Human GH (hGH) was first prepared and studied by Raben
- Shown to produce growth in sexually undeveloped adolescent

1959
- Retrieved HGH from human pituitaries given to presumed GHD patients
- 1 mg hGH was needed to treat one patient per day
- > 360 mg of hGH needed per patient per year

1963
- Immunoassay for hGH became available

1985
- Synthetic GH became available

Blizzard, Indian J Pediatr 2012 79 (1): 87-91
Raben MS. JCEM, 1958; 18:901-3
Key History and Physical Examination Findings Indicating Growth Hormone Deficiency can be Present

• Neonate with
  • Hypoglycemia
  • Prolonged jaundice
  • Microphallus
  • Traumatic delivery
• Cranial irradiation
• Head trauma
• Central nervous system infection
• Consanguinity
• Craniofacial midline abnormalities
• Severe short stature < -3 SD
• A height velocity below -2 SD over 1 year
• A height velocity more than 1.5 SD below the mean sustained over 2 years
• Signs of multiple pituitary hormone deficiency
• Signs indicative of intracranial lesion

Kappy et al. Pediatric Practice Endocrinology, Normal Growth and Growth Disorders, 56
Brain Magnetic Resonance Imaging as First-Line Investigation for Growth Hormone Deficiency Diagnosis in Early Childhood

• Retrospective cohort 68 children diagnosed with growth hormone deficiency (GHD) before 4 years of age
  – 43 boys & 25 girls
  – 1998-2012

• Diagnosis established by pharmacological GH stimulation tests
  – Exception of newborns with clinical signs of GHD

• Results 37 children were diagnosed with isolated GHD and 31 with multiple pituitary hormone deficiency (MPHD)

• Prevalence of abnormal MRI in whole cohort was 91.2%

• All patients diagnosed during the first 2 years of life had abnormal MRI findings
  – Prevalence of complex defects
    • First year of life- 94.1%
    • Second year of life- 75%

• Brain MRI may represent first-line investigation for diagnosing GHD in infancy and early childhood

**Fig. 1.** Age distribution of the different MRI findings in children with either IGHD or MPH.
Nonalcoholic fatty liver disease in adult hypopituitary patients with Growth Hormone deficiency and the impact of Growth Hormone Replacement Therapy

• 69 Japanese adult hypopituitary patients with GHD
• The prevalence of NAFLD in hypopituitary patients with GHD was significantly higher than in controls (77% vs 12%, P<0.001)
• Of 16 patients assesses by liver biopsy
  –14 (21%) were diagnosed with NASH
• GH replacement therapy
  –significantly reduced serum liver enzyme concentrations
  –Improved histological changes in the liver
  –Reduction of fibrotic marker concentrations in patients with NASH
Causes of pituitary deficiency in the patients with or without NAFLD

Figure 1 Serum aspartate aminotransferase and alanine aminotransferase, and γ-GTP concentrations before and after GH replacement therapy for 6 months in adult patients with GHD.

Figure 3 (A) Histological analysis by Masson's trichrome staining of the liver before and after GH replacement therapy in NASH patients with GHD (cases 1–5 in Table 2).

Laron Syndrome (LS)
Primary Growth Hormone Resistance or Insensitivity

- 3 sibling with marked short stature were evaluated by Dr. Laron in 1958
- Resembled children with hypopituitarism

• Boy is 3.5 years and the girl is 1.5 years old

Laron Syndrome (LS) Inheritance

- Consanguineous Jewish family of Yemenite origin
  - Parents grandparents were first cousins
  - Five older siblings of normal stature

- Laron later found that almost all the patients belonged to consanguineous families
- Conclusion that LS is caused by fully penetrant autosomal recessive mechanism

• Overnight fasting GH levels are high
• Nocturnal pulses reach 200-300 ng/ml
• Pituitary gland not enlarged
• Serum IGF 1 is undetectable
• No rise with hGH

Laron Syndrome (LS)  
Primary Growth Hormone Resistance or Insensitivity

• In 1984 biopsied liver of two patients  
• Showed that $^{125}$IhGH does not bind to GH-Rs  
• Found molecular defects residing in growth hormone receptor  
  – Majority in extracellular domain of the receptor  
  – Exons 2-7 and introns  
  – Results in absence of circulating GH binding protein  
• Inability of IGF 1 regeneration  
• Since then several hundred cases discovered worldwide  
• Majority of cases from the Mediterranean or from Ecuador

Protruding forehead
Sparse hair
Saddle nose
Small chin

small head circumference in untreated girl with LS

Anterior skull xray
Small bicondylar diameter
LS
Small facial bones

Delayed teething and defective, broken, crowded teeth in 9 year old LS

Laron Z, JCEM, 1031-44, 2004
Treatment Laron Syndrome

- Final heights range 116 and 142 cm males
- 108 and 136 cm in females
- Recombinant biosynthetic IGF 1 available since 1986
  - First year of growth the most
  - Growth velocity not as intense as that of GH

## FDA-Approved Conditions for the Use of Growth Hormone Therapy for Short Stature

<table>
<thead>
<tr>
<th>Condition</th>
<th>Year approved by FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood growth hormone deficiency</td>
<td>1985</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>1993</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>1997</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>2000</td>
</tr>
<tr>
<td>Born small for gestational age</td>
<td>2001</td>
</tr>
<tr>
<td>Idiopathic short stature</td>
<td>2003</td>
</tr>
<tr>
<td>SHOX gene deficiency</td>
<td>2006</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>2007</td>
</tr>
</tbody>
</table>

*FDA = US Food and Drug Administration.*
### FDA-Approved Indications for Growth Hormone Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Hormone Deficiency</td>
<td>0.16-0.3 mg/kg/wk</td>
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<tr>
<td>Prader Willi Syndrome</td>
<td>Up to 0.24 mg/kg/wk (or body surface area-based dosing at 1 mg/m² BSA/day)</td>
</tr>
<tr>
<td>SGA/IUGR</td>
<td>Up to 0.48 mg/kg/week</td>
</tr>
<tr>
<td>Turner Syndrome</td>
<td>Up to 0.33-0.47 mg/kg/week</td>
</tr>
<tr>
<td>Noonan Syndrome</td>
<td>Up to 0.066 mg/kg/day</td>
</tr>
<tr>
<td>Idiopathic Short Stature</td>
<td>Up to 0.47 mg/kg/week</td>
</tr>
<tr>
<td>Shox Deficiency</td>
<td>Up to 0.35 mg/kg/wk</td>
</tr>
</tbody>
</table>

Adverse events associated with Growth Hormone Therapy

- Intracranial hypertension (pseudotumor cerebri)
- Edema
- Slipped Capital femoral epiphysis
- Worsening of scoliosis
- Hyperglycemia

• This is your first visit with Tina E. Small.
• She is a 30 month old girl who was referred for evaluation of short stature.
• She was born at 34 weeks gestation with a weight of 2100 grams and length of 43 cm.
• Mother is 5’1” and father is 5’5”.
Premature infant with catch up growth
Marked acceleration of height and weight in the first 3-6 months, then paralleling the normal growth curve.
Normal weight for length, normal BMI
Normal growth velocity
Normal bone age
• SGA defined as having birth weight and/or length less than 2 standard deviations below the mean given their gestational age and sex (below 3%)
• Majority of these children experience a normal growth pattern

• 10% to 20% fail to show linear catch-up growth by 2 to 3 years of age

• Mean final adult height in SGA babies is reduced by 3-4 cm compared to mid parental height.

• Endocrine disorders associated with being born SGA
  – Premature adrenarche
  – Insulin resistance
  – Ovarian hyperandrogenism
  – Reduced pubertal growth

• Adults born SGA have increased risk for
  – Type 2 diabetes mellitus
  – Hypertension
  – Cardiovascular disease

• Tracy M is 8 years old and comes with her mother, who wanted to find out why she is not growing like her peers. She seemed to grow normally until age 2 but later it became obvious that she was falling behind. She reports no complaints. The family moved to California 6 months ago. Based on what you have learned, you remember the importance of assessing the height and weight over time, so you request her previous records. In the meantime, you consider several possibilities:

What is your differential diagnosis?
• Genetic short stature
• Constitutional growth delay
• Turner’s syndrome
• Hypothyroidism
• Growth Hormone deficiency
• Cushing’s syndrome
Which growth chart typical for Turner Syndrome?
Turner Syndrome

- Common chromosomal disorder

- Affects approximately 1 in 2000 females

- Short stature and ovarian dysgenesis in females two main characteristics

- Many organ systems can be affected

- Single X chromosome and absence of all or part of the second sex chromosome

- Majority (99%) of these spontaneously abort usually during first trimester of pregnancy

Saenger et al. *JCEM* 86: 3061-3069, 2001

Davenport. *JCEM* 95: 1487-1495, 2010

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Physical</th>
<th>Medical</th>
<th>Putative lymphatic gene</th>
<th>Germ cell survival genes</th>
<th>Other/unknown</th>
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<tbody>
<tr>
<td>Greater than 50%</td>
<td>Short stature</td>
<td>Growth failure</td>
<td>Low posterior hairline</td>
<td>Infertility</td>
<td>Learning disability</td>
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<td></td>
<td>Prominent ears</td>
<td>Chronic otitis media</td>
<td>Lymphedema</td>
<td>Gonadal failure</td>
<td>Unfavorable body composition</td>
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<td>Retrognathia</td>
<td>Low BMD</td>
<td>Nail dysplasia</td>
<td>Delayed puberty</td>
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<td></td>
<td>Narrow palate</td>
<td>Fractures</td>
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<td>25–50%</td>
<td>Cubitus valgus</td>
<td>Feeding problem</td>
<td>Webbed neck</td>
<td>Renal malformation</td>
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<td>Short fourth metacarpals</td>
<td>Sensorineural hearing loss a</td>
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<td>Hypertension</td>
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<td>Ptosis a</td>
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<td>Multiple nevi</td>
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<td>Strabismus a</td>
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<td>10–25%</td>
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<td>Obstructive sleep apnea</td>
<td>Single palmar crease</td>
<td>Hypothyroidism</td>
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<td>Scoliosis</td>
<td>Articulation problems</td>
<td>Inverted nipples a</td>
<td>Aortic coarctation</td>
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<td>Kyphosis</td>
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<td>Bicuspid aortic valve</td>
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<td>Pectus excavatum</td>
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<td>Increased liver enzymes</td>
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<td>Diabetes mellitus</td>
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<td>Celiac disease</td>
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<td>Inflammatory bowel disease</td>
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<td>von Willebrand’s disease</td>
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<td>JRA</td>
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<td>Pilomatrixoma</td>
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<td>Aortic dissection</td>
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<td>Prolonged QT</td>
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<td>Flat feet</td>
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<td>Hyperacusis</td>
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<td>Genu valgum</td>
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<td>Madelung deformity</td>
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<td>Patellar dislocation</td>
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JRA, Juvenile rheumatoid arthritis.

a Relationship to haploinsufficiency not well established.
<table>
<thead>
<tr>
<th>Problems</th>
<th>Screening test/referral</th>
<th>At Dx</th>
<th>Q visit</th>
<th>Q year</th>
<th>Other</th>
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<tbody>
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<td>Hip dislocation</td>
<td>Physical examination (including height, weight, BP, and calculation of BMI)</td>
<td>X</td>
<td>In infancy</td>
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<tr>
<td>Feeding problems</td>
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<td>X</td>
<td>In infancy</td>
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<tr>
<td>Strabismus</td>
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<td>X</td>
<td>4 months to 5 yr</td>
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<td>Otitis media</td>
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<td>X</td>
<td>All childhood</td>
<td></td>
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<td>Growth failure</td>
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<td>Pubertal delay</td>
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<td>Adolescence</td>
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<td></td>
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<tr>
<td>Lymphedema</td>
<td></td>
<td>X</td>
<td>Lifelong</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>X</td>
<td>Lifelong</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs information/support</td>
<td>Refer to TSS, other support groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural renal abnormalities</td>
<td>Renal ultrasound</td>
<td>X</td>
<td></td>
<td>Q 5–10 yr</td>
<td></td>
</tr>
<tr>
<td>Cardiac abnormality&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Examination by cardiologist; EKG; MRI/echo</td>
<td>X</td>
<td></td>
<td>Q 1–3 yr</td>
<td>At ages 0.5–3 and 10–12 yr</td>
</tr>
<tr>
<td>Conductive and SNHL</td>
<td>Formal audiology exam</td>
<td>X</td>
<td></td>
<td>At 1–1.5 yr</td>
<td></td>
</tr>
<tr>
<td>Gonadal dysfunction</td>
<td>FSH, LH</td>
<td>X</td>
<td></td>
<td>Q 2–5 yr (begin about age 4 yr)</td>
<td></td>
</tr>
<tr>
<td>Strabismus and hyperopia</td>
<td>Formal eye examination</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Serum IgA, TTG IgA Ab</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>T₄, TSH</td>
<td>X</td>
<td></td>
<td></td>
<td>Begin about age 4 yr</td>
</tr>
<tr>
<td>Developmental, educational, social problems</td>
<td>Developmental, educational, and/or psychosocial examination</td>
<td>X</td>
<td></td>
<td></td>
<td>Before school entry</td>
</tr>
<tr>
<td>Palatal/occlusive abnormalities</td>
<td>Orthodontic evaluation</td>
<td></td>
<td></td>
<td></td>
<td>At age 7 yr</td>
</tr>
<tr>
<td>Sexuality; school and/or work plans</td>
<td>Counseling</td>
<td></td>
<td></td>
<td></td>
<td>Begin about age 10 yr</td>
</tr>
<tr>
<td>Renal and liver dysfunction</td>
<td>Cr, BUN, LFTs, CBC</td>
<td>X</td>
<td></td>
<td>Begin about age 15 yr</td>
<td></td>
</tr>
<tr>
<td>Metabolic dysfunction</td>
<td>Fasting BG and lipids</td>
<td></td>
<td></td>
<td>Begin about age 15 yr</td>
<td></td>
</tr>
<tr>
<td>Low BMD GH action</td>
<td>DEXA scan; IGF-IGFBP-3</td>
<td></td>
<td></td>
<td>At about age 18 yr</td>
<td></td>
</tr>
</tbody>
</table>

BG, Blood glucose; BUN, blood urea nitrogen; CBC, complete blood count; cr, creatinine; Dx, diagnosis; DEXA, dual-energy x-ray absorptiometry; echo, echocardiogram; EKG, electrocardiogram; IGFBP-3, IGF binding protein-3; LFT, liver function test; SNHL, sensorineural hearing loss; TTG IgA Ab, tissue transglutaminase IgA antibodies; Q, every; tx, treatment.

<sup>a</sup> These guidelines were adapted from Davenport and Calikoglu (40) and Bondy (a guideline of the Turner Syndrome Study Group) (10) and reflect the author’s clinical practice. They suggest minimal routine screening evaluations. If the patient has a problem in one or more areas, she will generally be followed up by a specialist in those areas and evaluated more frequently.
• Growth failure problems for virtually all individuals with Turner Syndrome\textsuperscript{1}

• Untreated individuals achieve an average adult stature 20 cm shorter than peers\textsuperscript{1}

• Growth failure begins in utero, continues infancy and childhood

• Absence of pubertal growth spurt\textsuperscript{2}

• Growth hormone therapy is standard of care

• Randomized control trial in which girls treated with growth hormone for mean 5.7 years averaged 7.2 cm taller than those in the control group\textsuperscript{3}

Davenport, JCEM 92:3406-3416, 2007\textsuperscript{1}
Davenport, JCEM 95: 1485-1495, 2010\textsuperscript{2}
Stephure et al. JCEM 90:3360-3366, 2005\textsuperscript{3}
TABLE 3. Pubertal induction and maintenance estrogen therapy using TDE: a protocol using low growth-promoting doses for 18–24 months

<table>
<thead>
<tr>
<th>Treatment (months)</th>
<th>Target E2 (pg/ml)</th>
<th>E2 dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3–4</td>
<td>0.1 µg/kg</td>
<td>Consider initiation of puberty at age 11–12 yr if there is no breast development. Cut and apply a portion of a matrix patch to deliver 0.1 µg/kg E2. Apply in p.m. and remove in a.m.</td>
</tr>
<tr>
<td>6</td>
<td>3–4</td>
<td>0.1 µg/kg</td>
<td>Wear a 0.1 µg/kg equivalent portion of the patch continuously. Change patch as directed (once or twice weekly). Check random E2 level to ensure E2 is in target range.</td>
</tr>
<tr>
<td>12</td>
<td>~6–8</td>
<td>0.2 µg/kg</td>
<td>E2 levels below this are believed to accelerate growth more than bone maturation.</td>
</tr>
<tr>
<td>18</td>
<td>~12</td>
<td>12.5 µg</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>~25</td>
<td>25 µg</td>
<td>Start progestin (earlier, if breakthrough bleeding occurs): 200–300 mg micronized oral progesterone for about 12 d/month qhs (causes drowsiness) or 5 mg oral medroxyprogesterone for about 12 d/month.</td>
</tr>
<tr>
<td>30</td>
<td>~37</td>
<td>37.5 µg</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>~50</td>
<td>50 µg</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>~75</td>
<td>75 µg</td>
<td>Typical adult dose; may not be high enough to protect liver, arteries, etc.</td>
</tr>
<tr>
<td>48</td>
<td>50–150</td>
<td>100 µg</td>
<td></td>
</tr>
</tbody>
</table>

E2, 17β-Estradiol; qhs, before bedtime.

This protocol is but one of many that can be used. This specific protocol is used in the author’s clinic and individualized, depending on patient circumstances and desires. For example, older girls may want to be started at 25 µg.

To convert picograms per milliliter to picomoles per liter, multiply by 3.671. E2 levels should be monitored using liquid chromatography/tandem mass spectroscopy technology.

Vivelle Dot, matrix transdermal patch, is small and tends to adhere well. One-sixth to one-eighth of a 25 µg patch is approximately 0.1 µg/kg dose.
• Double-Blind Placebo Controlled trial 1987 to 2003 (enrollment closed 1996)
• 149 girls
• 5 years to 12.5 years of age
• Four groups
  – Double placebo
  – Estrogen alone
  – Growth hormone-estrogen group
  – Growth hormone-alone group
• Dose of Ethinyl Estradiol:
  – 25 ng/kg/day children 5 to 8 years
  – 50 ng/kg/day 8 to 12 years age
• At first visit after age 12 years patients received escalating doses of ethinyl estradiol
• Adult height was greater in growth hormone-estrogen group than in growth hormone alone group
  – 0.32 ± 0.17 standard deviation score (2.1 cm) (P=0.059)
• Modest synergy between childhood low-dose estradiol and growth hormone
B

**Adult-Height Population**

![Graph showing the change in height SDS over years in study for different groups: Growth hormone-estrogen, Growth hormone alone, Estrogen alone, Double placebo.](image)

<table>
<thead>
<tr>
<th>Years in Study</th>
<th>Growth hormone-estrogen</th>
<th>Growth hormone alone</th>
<th>Estrogen alone</th>
<th>Double placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>0.5</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.0</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>2</td>
<td>0.0</td>
<td>-0.5</td>
<td>-1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>3</td>
<td>-0.5</td>
<td>-1.0</td>
<td>-1.5</td>
<td>-1.5</td>
</tr>
<tr>
<td>4</td>
<td>-1.0</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
</tr>
<tr>
<td>5</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
</tr>
<tr>
<td>6</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
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<tr>
<td>7</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
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<tr>
<td>8</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
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<tr>
<td>9</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
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<tr>
<td>10</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
</tr>
<tr>
<td>11</td>
<td>-1.5</td>
<td>-1.5</td>
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</table>

**No. of Patients**

<table>
<thead>
<tr>
<th></th>
<th>25</th>
<th>25</th>
<th>25</th>
<th>25</th>
<th>25</th>
<th>25</th>
<th>22</th>
<th>15</th>
<th>12</th>
<th>9</th>
<th>7</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone-estrogen</td>
<td>27</td>
<td>27</td>
<td>26</td>
<td>26</td>
<td>25</td>
<td>22</td>
<td>23</td>
<td>22</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>9</td>
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<tr>
<td>Growth hormone alone</td>
<td>21</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>21</td>
<td>17</td>
<td>15</td>
<td>11</td>
<td>7</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Estrogen alone</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>13</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
• The clinical significance of the short stature depends on several factors:
  – genetic potential
  – growth velocity

• The two most common causes of short stature
  – familial short stature
  – constitutional delay of growth

• An estimate of a child's adult height potential can be obtained by the midparental height

• The history and physical examination should include
  – family history of growth and pubertal onset
  – Review of systems for features suggestive of gastrointestinal, pulmonary, immunologic, or other systemic disease

• Children with short stature and normal growth consider evaluation with bone age

• Children with severe short stature (eg, height ≤-2.5 SD [0.6th percentile]) or growth failure should be further evaluated