

Clues to Unraveling the Mystery of Central Precocious Puberty

- Unraveling the Myths

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Guided Case Studies With Dr. Smith, our General Pediatrician and Dr. Palmer, our Pediatric Endocrinologist

- Each myth will be presented and unraveled with supportive data
- This section will focus on interactions between a general pediatrician or pediatric endocrinologist, parent and the child suspected of having CPP
 - The doctor (Dr. Smith) will use his basic understanding of CPP and the considerations reviewed to assess and determine if the patient has CPP
 - Provide guidance and support for the parent to make decisions on treatment plans
- The variations in the progression of puberty often feel like a mystery to parents and pediatricians
- This section will address some clues to unraveling the mystery of CPP

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Myth #1

Chronological age distinguishes normal variation from central precocious puberty



Unraveling Myth #1

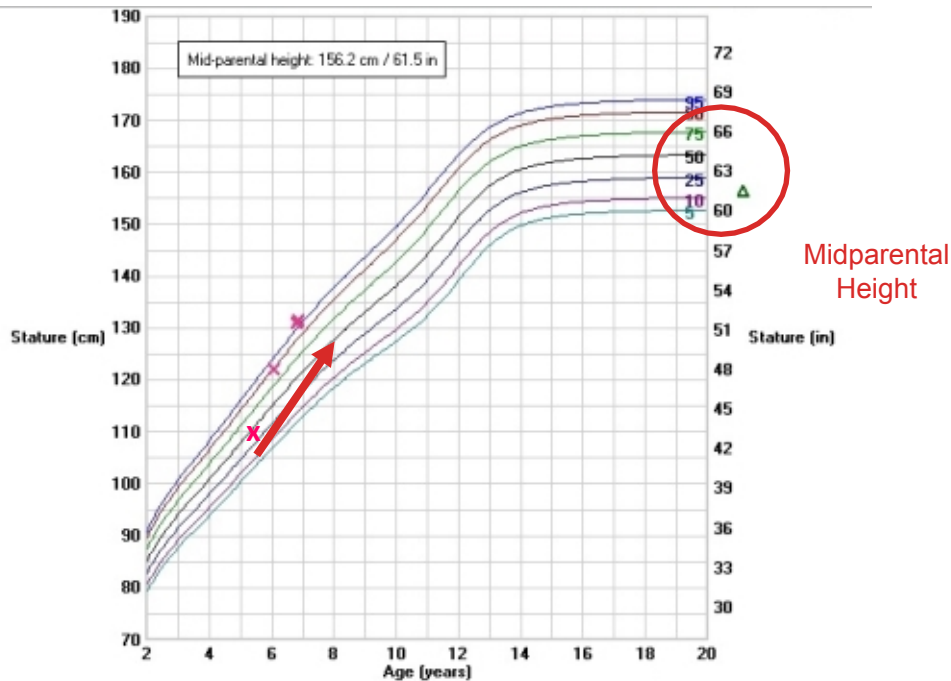
- There are many factors that influence the onset of puberty
- Although age is helpful, it's not diagnostic
- Compare chronological age to bone age and height age
- Rate of progression is key



References: 1. Aylwin CF, Toro CA. *J Res Adolesc.* 2019;29(1):54-79. 2. Wei C, Crowne EC. *Arch Dis Child.* 2016;101(5):481-488. 3. Wohlfahrt-Veje C et al. *J Clin Endocrinol Metab.* 2016;101(7):2667-2674. 4. Livadas S, Chrousos GP. *Curr Opin Pediatr.* 2016;28(4):551-558. 5. Soliman A et al. *Indian J Endocrinol Metab.* 2014;18(suppl 1):S39-S47. 6. Herman-Giddens ME et al. *Pediatrics.* 1997;99:505-512. 7. Villamor E, Jansen EC. *Annu Rev Public Health.* 2016;37:33-46. 8. Simon D. *Horm Res.* 2002;57(suppl 2):53-56.

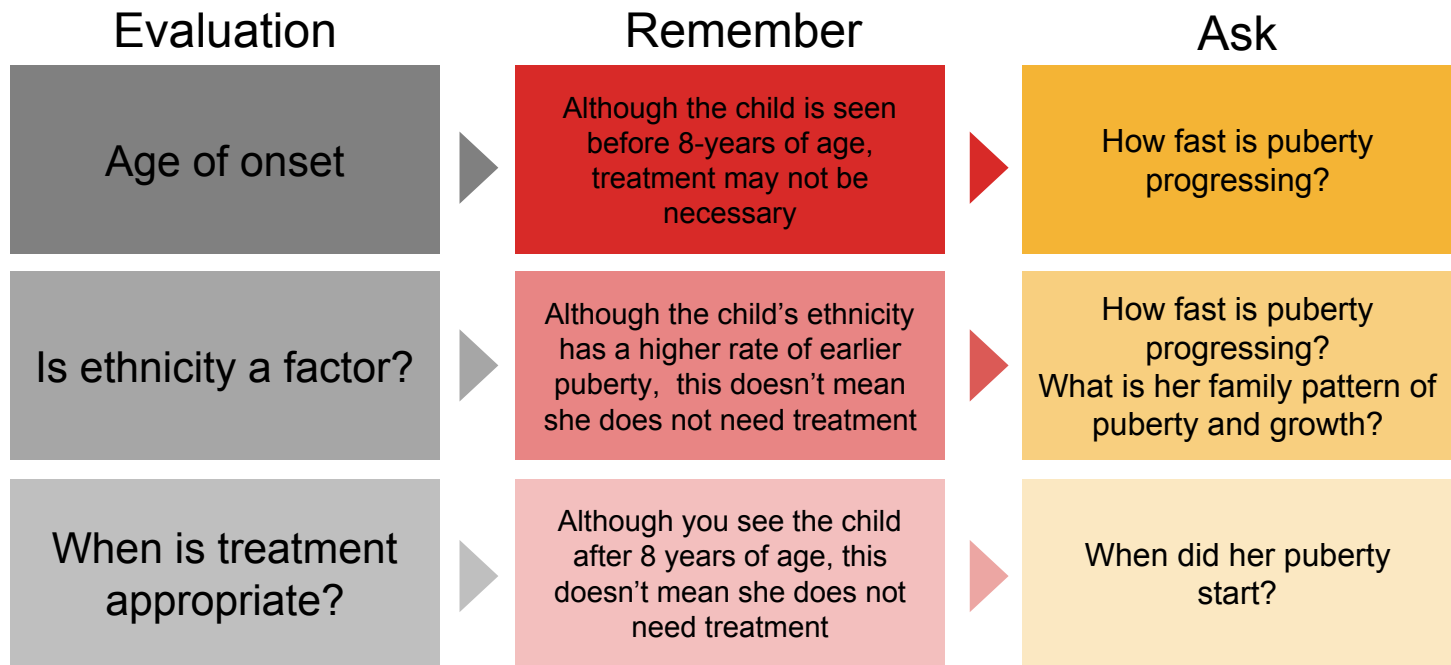
Age vs Growth Chart Velocity Is an Important Clue in Diagnosing CPP

Stature-for-age Percentiles (Girls, 2 to 20 years)^a



Identify Rapid Pubertal Progression and Who Needs to Be Referred

Careful evaluation of rate of progression



Case Study 1



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Case Study 1: Dr. Smith's Evaluation



- 6 y 4 m old girl
- Breast onset at age 6 y
- Pubic area Tanner stage 2
- Height 95%
 - Consistently
- Bone age 7 y 6 m
- Predicted height equals midparental height
- By age 7 years, breasts still Tanner stage 2, bone age 8 y

Case Study 1: Dr. Smith's Observations and Discussion With Parent

What is your diagnosis?

- A. Central precocious puberty
- B. Normal puberty
- C. Premature thelarche

- Breast onset **at age 6 y**
- Pubic area Tanner stage 2
- Height 95%
 - **Consistently**
- Bone age 7 y 6 m
- Predicted height **equals midparental** height
- By age 7 years, **breasts still Tanner stage 2**, bone age 8 y

Case Study 1: Dr. Smith's Diagnosis

- In this case, the child presents with early but normal puberty
- The child's rate of progression is slow
- Dr. Smith recommends they should monitor the child closely and to note any new changes
- Important to next visit to be in 3 – 6 months, not wait a full year for next well child visit

Myth #2

- Treatment is valuable as long as it is started prior to menarche
- Growth stops at menarche

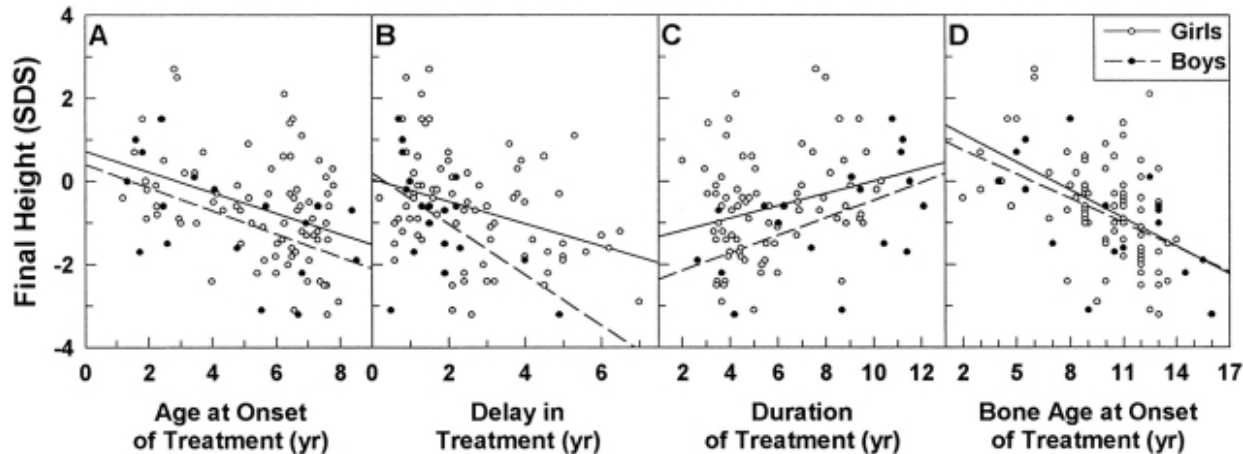


Unraveling Myth #2

- Referring early is important for preserving predicted adult height (PAH)
 - Better height outcomes are achieved when treatment is started earlier
- With rapidly progressing patients, you could miss the window to treat resulting in a shorter adult height
- The onset of menarche does not mean the end of growth potential (need to assess bone age and growth rate)
 - Treatment to stop menses can still occur after onset of the first period

Tall stature *now* does not mean tall stature *later*

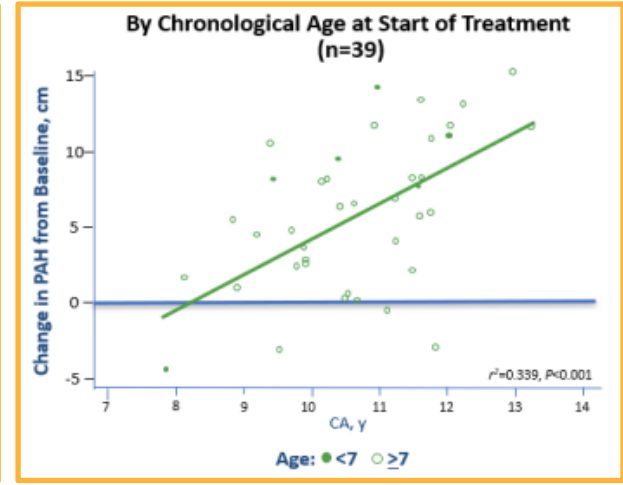
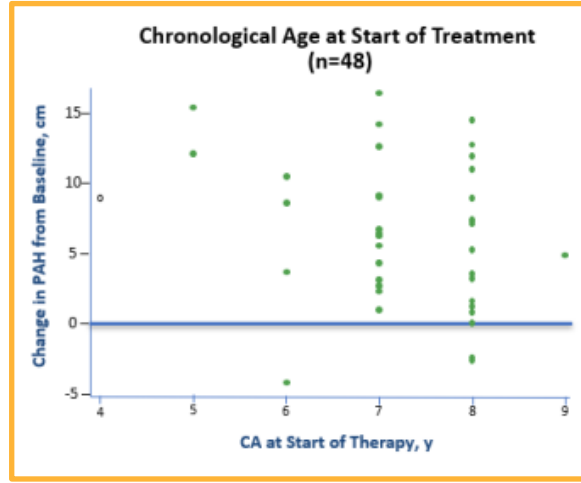
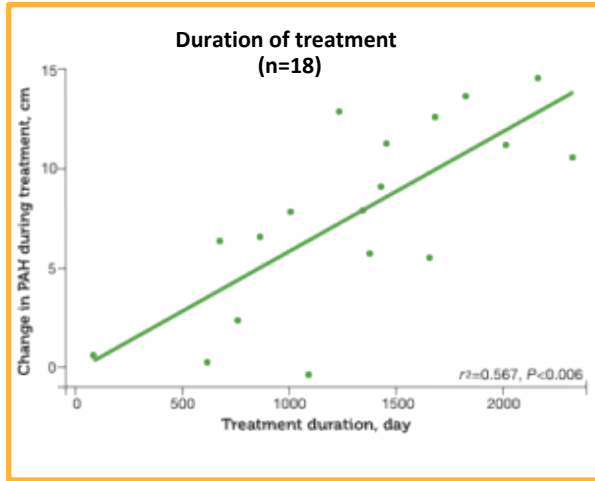
Taller Height Outcomes Are Achieved When Treatment Is Started Earlier^a



- Less delay in the onset of treatment, younger chronological and bone age led to greater final height
- Final height correlated with duration of treatment

^a In a study of 98 children (80 girls, 18 boys) with LHRH dependent precocious puberty treated with LHRH agonist beginning at age 5.3 ± 2.1 years old for an average of 6.1 ± 2.5 years, final height was evaluated. 36 girls started treatment before the age of 6 years.

Change in Predicted Adult Height During Treatment^a



- PAH continued to increase with longer duration of treatment
- Treatment is effective even in children who start after 7 years of age
 - PAH continued to increase in 45/48 females, regardless of age at initiation of treatment
- PAH continued to increase irrespective of chronological age during treatment

^aIn a study of 48 girls with CPP breast onset < 8 yrs; peak stimulated LH ≥ 10 IU/L; CA < 9 yrs; BA > 1 y advanced treated with leuprolide acetate IM beginning at age 6.8 ± 1.9 (range 1-9) years old with assessments at weeks 4, 8, 12, 24, 36 and 48, and then every 6 months until the study drug was discontinued. The annual visits until 21 years of age. Final height was evaluated.

Factors influencing decision to start treatment

Starting treatment

- Girls with rapid progression of puberty have lower height outcomes than those with slow progression who may not need treatment
- Further decrease in PAH due to rapid bone maturation
- PAH compared to MPH
- Impending onset of menarche in girls

Case Study 2



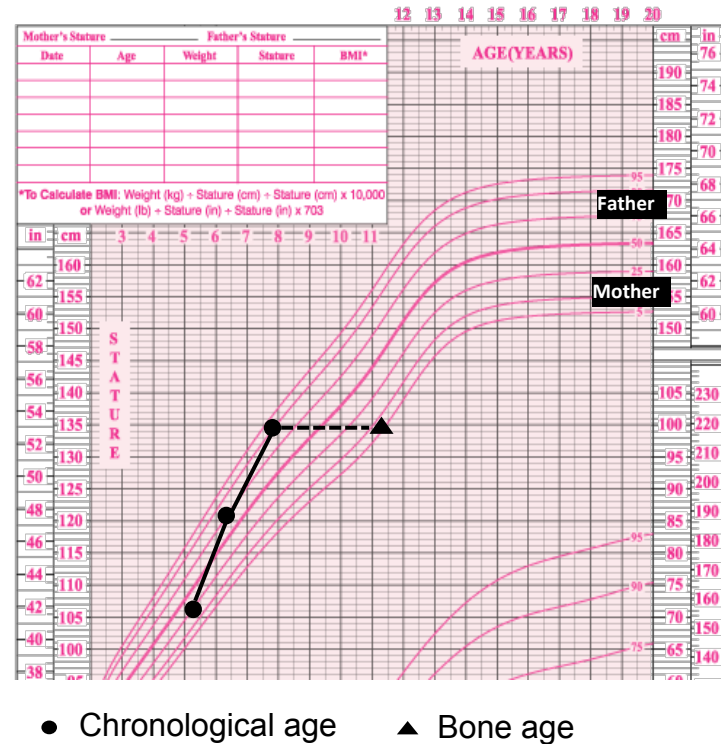
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Case Study 2: Dr. Smith's Initial Evaluation^a

- Girl (7.5 y old) with Tanner stage 3 breasts
- Bone age is at 11 y
- Family happy she is tall
- Would you refer?

Ask:

- When did puberty start?
- How rapidly is it progressing?
- How advanced is bone age?
- How advanced is puberty?



Case Study 2: Outcome Without Treatment or If Treatment Is Delayed^a

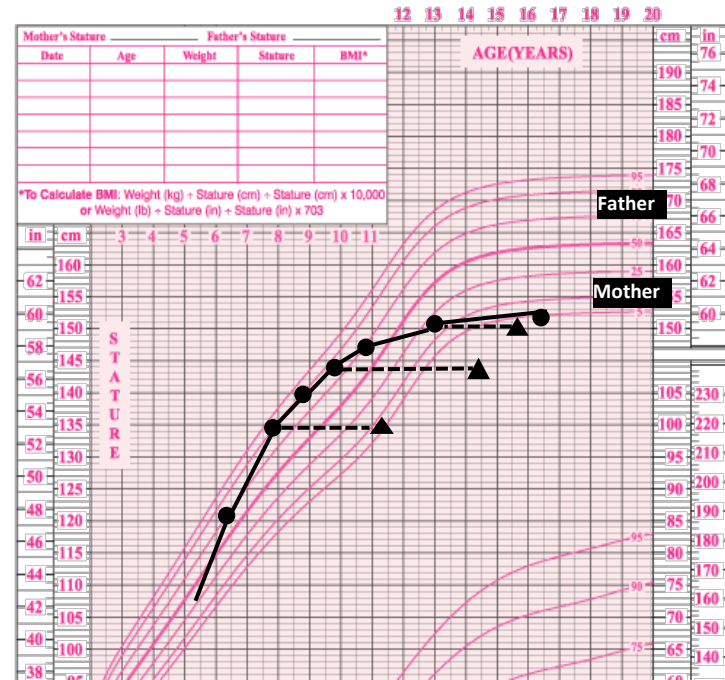
Recap:

- Girl (7.5 y old) with Tanner stage 3 breasts
- Bone age: 11 y old
- Family happy she is tall

Outcomes due to delay in treatment

- Breast development started at 5.5 years old – **referral delayed**
- Menarche occurred at 11 years of age
- Bone age was recorded to be at 14 years of age by then – **so too late to treat**

Final height not quite 5'0"



- Chronological age
- ▲ Bone age

Case Study 2: Outcome With Treatment^a

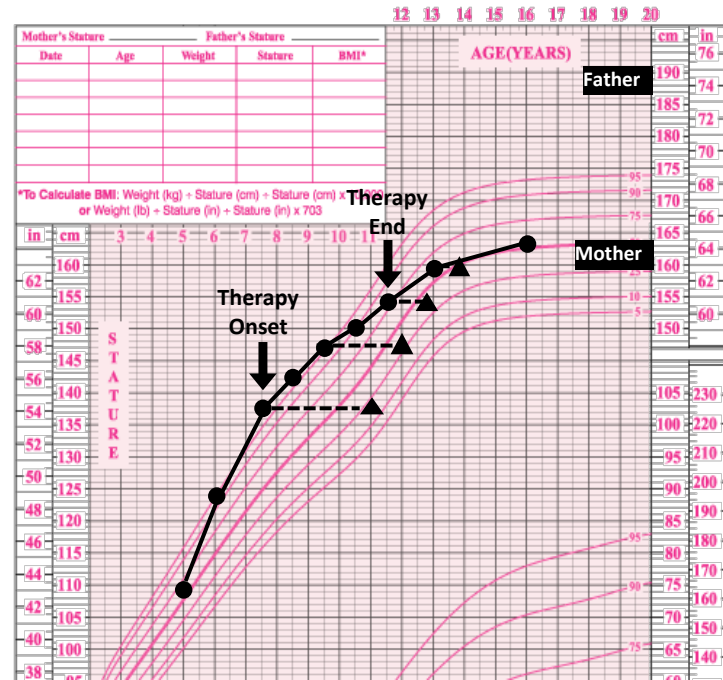
Recap:

- Girl (7.5 y old) with Tanner stage 3 breasts
- Bone age: 11 y old
- Family happy she is tall
- However, **bone age has advanced 3.5 years from her age**

Outcomes with early treatment:

- Bone age advance slows down
 - 1.5 years advanced by end of treatment
- Treatment was stopped at 12 y old
- After treatment, an additional 3 inches of growth was achieved
- Menarche: 13 y old

Final height consistent with family 5'4"



- Chronological age
- ▲ Bone age

Case Study 2: Summary of Care

- Treatment can improve final height in children with CPP
- Better patient outcomes may require:
 - Less delay starting treatment
 - Longer duration of treatment
 - Lower chronological age and bone age at start of treatment contribute to greater final height

Myth #3
Age 10-11 years is a good time to stop treatment since menarche will most likely occur around 11.5 years, which is normal



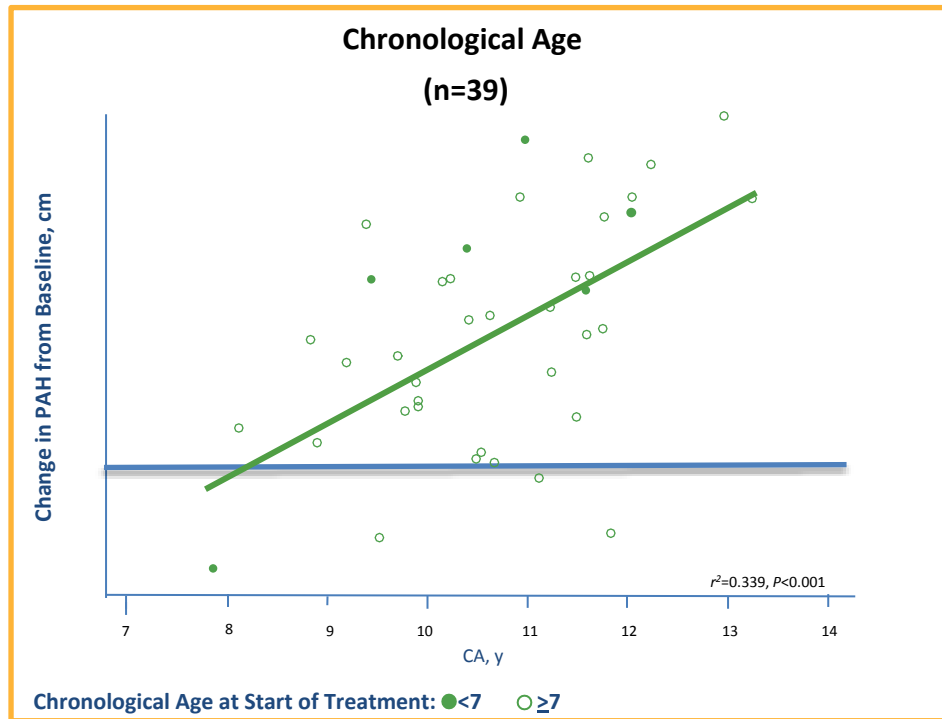
Unraveling Myth #3

- Determining an appropriate time to stop treatment is very important
 - Better outcomes with longer duration of treatment
 - For example, stopping at 10 years of age may compromise final height if bone age shows continued growth potential

Pediatrician's role: If the endocrinologist recommends continuing treatment, help the family understand why.

Predicted adult height continued to increase irrespective of chronological age during treatment^a

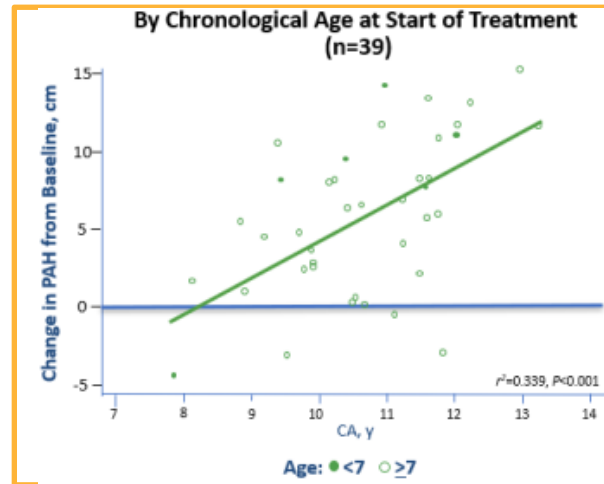
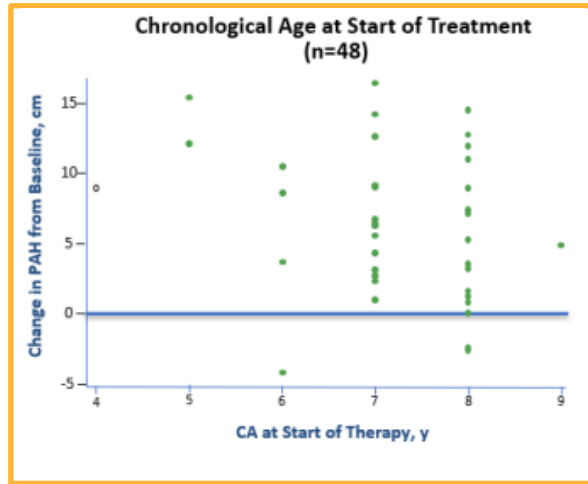
- Twenty-nine of the thirty-eight (76.3%) girls evaluated over one year showed increases in PAH during that year.
 - This was not dependent on whether CA equaled BA, the rate of BA advancement during that year, the GV during that year, or baseline PAH.
 - Predicted adult height increase over 1 year of treatment averaged 1.77 ± 2.21 (range, -2 to 8.47 cm) and was very similar for those with BA ≥ 12 years and those with BA < 12 years.
- Mean PAH continued to increase in 16/22 girls who continued treatment after a CA of 10 years (0.14–8.47 cm).



Solid dots indicate CA < 7 at start of treatment, open circles indicate CA ≥ 7 at start of treatment. CA, Chronological age; PAH, predicted adult height.

^aIn a study of 48 girls with CPP breast onset < 8 yrs; peak stimulated LH ≥ 10 IU/L; CA < 9 yrs; BA > 1 y advanced treated with leuprolide acetate IM beginning at age 6.8 ± 1.9 (range 1-9) years old with assessments at weeks 4, 8, 12, 24, 36 and 48, and then every 6 months until the study drug was discontinued. Then annual visits until 21 years of age.

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Predicted Adult Height in patients with a Bone Age of <12 years vs ≥12 years^a

- 84% (16/19) of girls who continued treatment after a BA of 12 years continued to have an increase in PAH (range 0.5-4.8 cm)
- The 3 girls who did not show improvement of PAH were either already at or near their MPH or exhibited poor growth

Comparison of girls with a BA of <12 years vs ≥12 years at final visit

Characteristics	<12 years at final visit	≥12 years at final visit
BA, n	16	31
Mean, years (range)	11.4 (7.6–12.0)	12.6 (12.0–13.5)
BA/CA, n	16	31
Mean (range)	1.2 (1.0–1.5)	1.1 (1.0–1.4)
Change in PAH during treatment	13	26
Mean, cm (range)	3.9 (-4.4–11.3)	6.5 (-2.9–14.6)

The mean increase in PAH during treatment was greater in girls with a BA of ≥12 years (6.5 cm) than in girls with a BA of <12 years (3.9 cm)

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BA, bone age; CA, chronological age; PAH, predicted adult height; MPH, Mid-parental height.

Reference: Trujillo MV et al. Importance of individualizing treatment decisions in girls with central precocious puberty when initiating treatment after age 7 years or continuing beyond a chronological age of 10 years or a bone age of 12 years [published online ahead of print, 2021 Apr 14]. *J Pediatr Endocrinol Metab.* 2021;10.1515

Clues on the Duration of GnRHa Therapy

- Mean age of treatment discontinuation: 10.6 - 12 years¹
- Mean bone age at discontinuation: 12.1 - 13.9 years¹
- Mean age of menarche: 12.3 years; on avg 1.5 years after treatment stopped¹
- Do not stop therapy prematurely— each case is specific and individualized^a
 - Positive outcomes include
 - Maximizing height
 - Synchronizing puberty with peers
 - Ameliorating physiological distress

^aThis evidence comes from Dr. Karen Klein's clinical and professional experience.
GnRHa, gonadotropin releasing hormone agonist.

Reference: 1. Carel JC et al. *Pediatrics*. 2009;123(4):e752-e762.

Factors influencing decision to stop treatment

Stopping treatment

- Desire to have pubertal progression concurrent with peers
- Resumed bone maturation acceleration posttreatment
- PAH and family height
- Loss of PAH after end of treatment
- In general, it is reasonable to continue treatment until PAH is close to MPH and growth is still reasonable.
- If GV continues to slow down, CA is nearing BA and PAH is not improving, then discontinuation of treatment is reasonable
- If BA indicates growth potential and PAH is improving, even GV alone may not dictate the cessation of treatment

Case Study 3



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Case Study 3: Pediatric Endocrinologist Dr. Palmer's Initial Evaluation



- Chronological age: 5 y old
- Breasts since 3 y old
- Pubic hair starting
- Bone age: 9 y old
- PAH 4'8"
- MRI of head – hypothalamic hamartoma

Case Study 3: Dr. Palmer's Treatment Evaluation

- GnRHa treatment should be started*
- At 10 years of age, the child is complaining and wants to stop treatment
 - She feels her friends are “growing faster”
- Bone age is still at 12 years of age
- Predicted height 5'1”

What is your advice about stopping or continuing treatment now?

Case Study 3: Dr. Palmer's Concerns About Stopping Treatment

- Predicted height will decrease after treatment is stopped if too early
- Her CA is not close to her BA to warrant stopping treatment
- What do you say to the mother and child?
 - While some girls her age are now starting with some breast development, your daughter is already in mid-puberty and that will resume when treatment is stopped
 - Although the average onset of menses occurs 18 months after cessation of treatment, some may start menses earlier, by 3–12 months after discontinuation of treatment
- Strongly recommend continuing treatment longer and stop when:
 - Age appropriate development for peers, rather than age of peers
 - Improved adult predicted height
 - CA close to BA, as long as growth rates continue to be reasonable
 - If growth rate slows below normal prepubertal rates, then consider stopping treatment

Myth #4

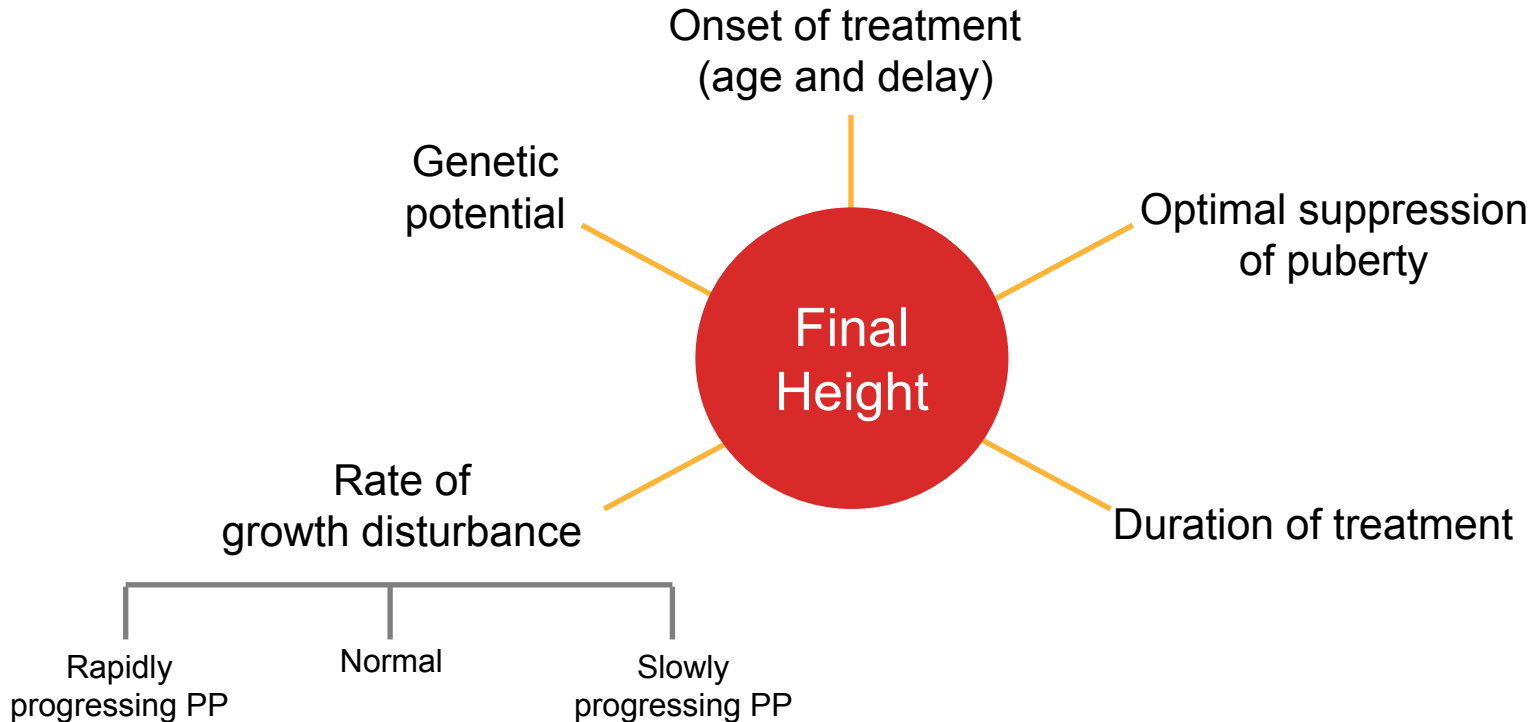
Treatment after 7 years of age does not increase adult height



Unraveling Myth #4

- Age of onset of puberty is key, NOT age of presentation for treatment
 - Girls with onset >7 years of age may need treatment
- Range of adult heights published is wide and variable
- Individual assessment of all factors are crucial

Clues and Factors Influencing Final Height



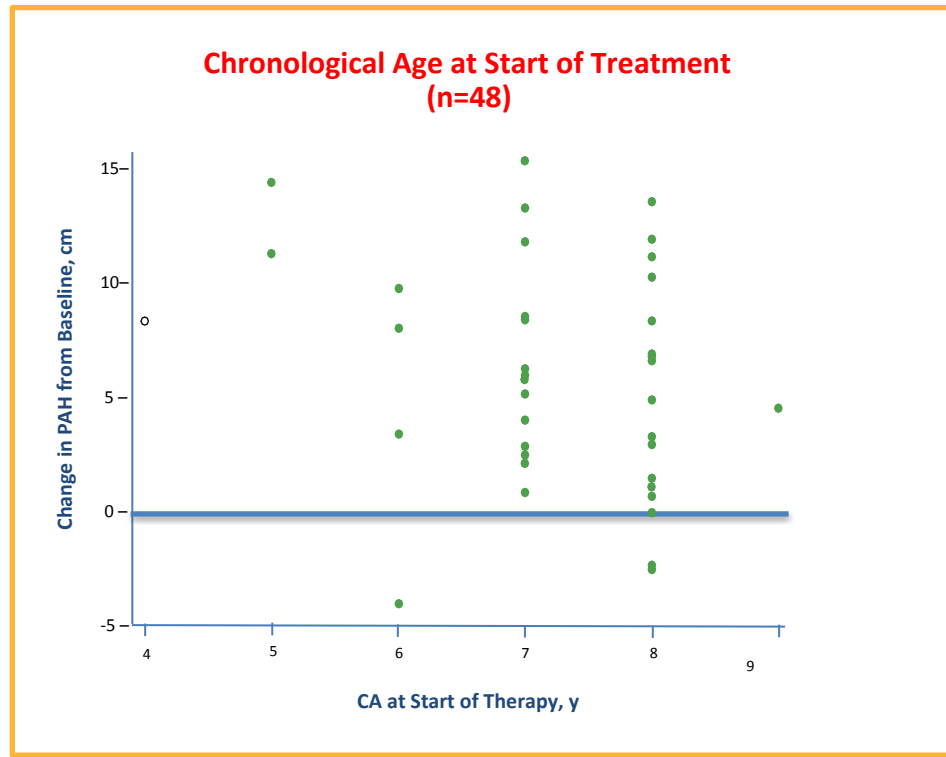
PP, precocious puberty.

Predicted adult height and chronological age of ≥ 7 years ^a

- Predicted adult height increased in 91% of girls who started treatment at a chronological age of ≥ 7 years
- **PAH continued to increase** in 45/48 females, **regardless of age** at initiation of treatment

^aIn a study of 48 girls with CPP breast onset < 8 yrs; peak stimulated LH ≥ 10 IU/L; CA < 9 yrs; BA > 1 y advanced treated with leuprolide acetate IM beginning at age 6.8 ± 1.9 (range 1-9) years old with assessments at weeks 4, 8, 12, 24, 36 and 48, and

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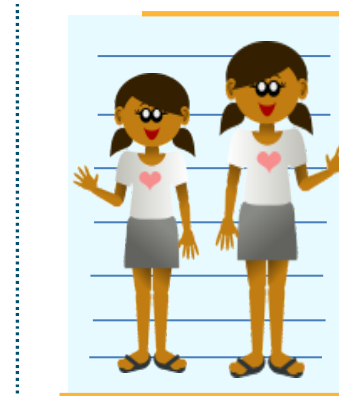


PAH, predicted adult height.

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Predicted adult height increased in the majority of girls who started treatment at a chronological age of ≥ 7 years^a

- 46% (17/37) of girls who initiated treatment at a CA of ≥ 7 years had a ≥ 5 cm increase in PAH
- 16% (6/37) of girls who initiated treatment at a CA of ≥ 7 years had a >10 cm increase in PAH
- 91% (30/33) of girls who initiated treatment at a CA of ≥ 7 years had improvement in PAH



PAH continued to increase in girls who continued treatment after a CA of 10 years, including in girls who started treatment with a CA of ≥ 7 years

^aIn a study of 48 girls with CPP breast onset < 8 yrs; peak stimulated LH ≥ 10 IU/L; CA < 9 yrs; BA > 1 y advanced treated with leuprolide acetate IM beginning at age 6.8 ± 1.9 (range 1-9) years old with assessments at weeks 4, 8, 12, 24, 36 and 48, and then every 6 months until the study drug was discontinued. Then annual visits until 21 years of age.

Summary



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Summary of Increase in Adult Height in Children With CPP Treated With GnRHa

- Earlier age of onset correlates to poor height outcomes if left untreated
- Early GnRHa treatment allows for greater height gain
- Some girls may have rapid progression→ have unfavorable outcomes
- Some girls will progress slowly and not need treatment
- Individualizing treatment decisions is important and no decisions should be based on age or bone age alone
 - PAH increase including in girls initiating treatment at chronological age < 7 years
 - PAH continued to increase in girls who continued treatment after CA 10 and slos after bone age 12

Rationale for Treatment of CPP With GnRHa

- Delay additional precocious pubertal development until an appropriate age
 - Prevent menses
- Children with CPP may encounter psychological/psychosocial issues that may result from having physical and statural development advance compared with same age peers
- Preserve or reclaim genetic growth potential