

# Central Precocious Puberty:

To Treat or Not to Treat  
and Other Clinical Dilemmas

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THE CHILDREN'S HOSPITAL OF PHILADELPHIA

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## Objectives

- ▶ Describe potential pharmacologic options for treating patients with central precocious puberty and identify appropriate use of these medications
- ▶ Discuss current practice styles and potential ways to either maintain or change current styles based on current research data

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## Defining Puberty

- ▶ Hormonally mediated transition between childhood and adulthood
- ▶ Goals of puberty
  - Development of secondary sexual characteristics
  - Achievement of adult height
  - Reproductive maturity
- ▶ Requires interaction between hypothalamus, pituitary, gonads, and internal sexual organs

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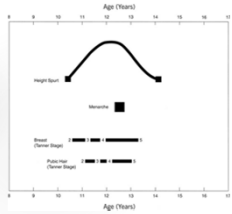
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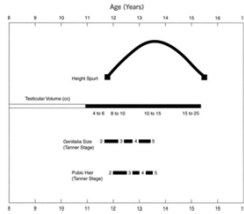
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## Sequence of Puberty

Average American Girls



Average American Boys



Tanner, J. M. (1975). Growth and endocrinology of the adolescent. In L. I. Gardner (Eds.) *Endocrine and genetic diseases of childhood and adolescents* (2nd ed., p. 14). Philadelphia, PA: Saunders.

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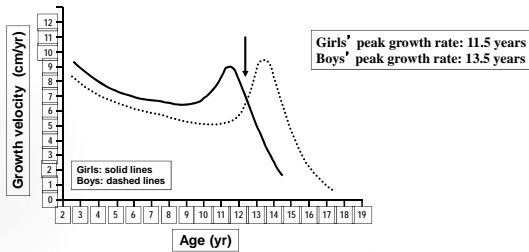
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## Pubertal Growth Spurt



Tanner, J. M., & Davies, P. S. (1985). Clinical longitudinal standards for height and height velocity for North American children. *Journal of Pediatrics*, 107, 317-329.

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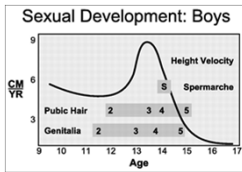
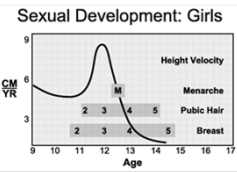
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## Pubertal Milestones with Growth Spurt Overlay




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## Pubertal Milestones

### ► Female

- Breast Development - 10 years
  - Range: 8-13 years
- Sexual Hair - 11 years
  - May precede breast development (10%)
- Menarche - 12.5 years

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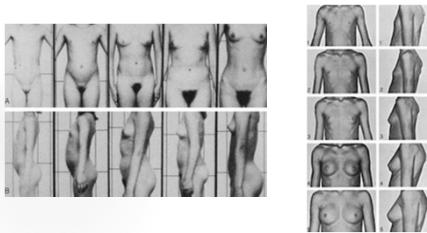
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## Physical Exam: Tanner Stages



Tanner, J. M. (1975). Growth and endocrinology of the adolescent. In L. I. Gardner (Eds.) *Endocrine and genetic diseases of childhood and adolescents* (2nd ed.). Philadelphia, PA: Saunders.

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## Pubertal Milestones

### ► Male

- Testicular Enlargement - 11 years
  - Range: 9-14 years
- Sexual Hair - 12 years
  - May precede testicular enlargement

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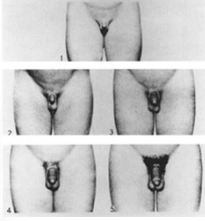
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## Physical Exam: Tanner Stages



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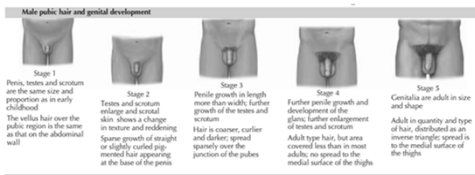
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## Physical Exam: Tanner Stages



► Resist describing children with “unitary Tanner stages”

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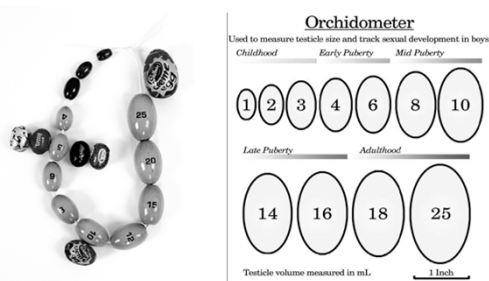
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## Physical Exam: Tanner Stages




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## What is Precocious Puberty?

- ▶ Females
  - Breast development before age 8 years old
- ▶ Males
  - Testicular enlargement before age 9 years old

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## Precocious Puberty (PP) Evaluation

- ▶ Physical exam!
- ▶ Diagnostic studies – first line
  - Gonadotropins
    - Morning ICMA (ultrasensitive) LH and FSH
  - Estradiol/testosterone
  - Bone age
- ▶ Diagnostic studies to consider:
  - GnRH/GnRHa stimulation testing
  - Thyroid Function Tests (TFTs)
  - MRI of pituitary gland

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## Central Precocious Puberty (CPP)

- ▶ Girls
  - Most often idiopathic (85%)
    - Physically and hormonally normal except for age of onset
  - Intracranial disorders (impair normal childhood suppression of hypothalamus)
    - CNS tumors (astrocytomas, gliomas, germinomas)
    - Myelomeningocele
    - Congenital anomalies (hamartomas)
    - Trauma
    - Postsurgical or postradiation

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## Central Precocious Puberty (CPP)

- ▶ Boys
  - More likely to be pathologic (up to 60%)
  - Also can be idiopathic

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## Potential Reasons to Treat with a GnRH Agonist

- ▶ Compromised Adult Height
- ▶ Psychosocial and Behavioral

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## Treatment for CPP GnRH Agonist Treatment

- ▶ Leuprolide (Lupron)
  - 3 month injection vs. monthly injection
  - IM injection
  - Cost: \$8,936-\$17,868 per year
    - Does not include cost to administer
  - Administered at PCP's office or Endocrinologist's office



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### Treatment for CPP GnRH Agonist Treatment

- ▶ Lupron Depot Dosing (1 - month formulation)
  - <25 kg: 7.5 mg
  - 25-37.5 kg: 11.25 mg
  - >37.5 kg: 15 mg
- ▶ Lupron Depot-Ped® (3 - month formulation):
  - 11.25 mg
  - 30 mg

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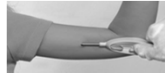
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### Treatment for CPP GnRH Agonist Treatment

- ▶ Annual histrelin implants (Supprelin)
  - Hydrogel implant delivery system
  - FDA approved for CPP in the US in 2007
  - Inserted under skin with brief sedation in surgery clinic
  - Releases histrelin for year
  - Replaced about every 12 months, prn
  - \$16,800/year
    - Does not include cost to place and remove



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### Treatment for CPP GnRH Agonist Treatment

- ▶ Supprelin Dosing
  - 50mg for children 2 years of age and older

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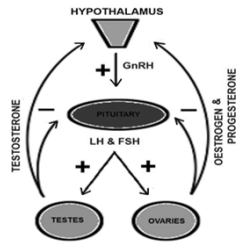
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## How Do GnRH Agonists Work?

- ▶ Low dose of continuous exposure vs. pulsatile GnRH
- ▶ Initial stimulatory effect, followed by suppression due to GnRH receptor insensitivity



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## GnRH Agonist Treatment What to Expect

- ▶ Initial stimulatory effects
- ▶ No further breast development/testicular enlargement or potential regression
- ▶ Decrease in growth velocity
- ▶ No effect on pubic hair

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## Side Effects of GnRH Agonist

- ▶ Injection site reaction
- ▶ Hot flashes
- ▶ Weight gain
- ▶ No significant long-term effects
  - Decreased bone mineral density
- ▶ Normal puberty returns on average 16 months after completion of therapy

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### Case Study: Annie Clinical Presentation

- ▶ 5 years 4 months old female
- ▶ Tanner 3 breast development, Tanner 2 pubic hair
- ▶ Linear growth at 95th%ile
  - Increase in growth velocity?
- ▶ Family history of early puberty

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### Case Study: Annie Evaluation

- ▶ TFTs normal
- ▶ Gonadotropins not completed as ordered
- ▶ Stimulation testing confirmed CPP – peak LH of 5.8 mIU/ml
- ▶ Bone age advanced by 2 years
- ▶ MRI of the pituitary gland normal

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### Case Study: Annie Treatment

- ▶ Treated for psychosocial reasons and height preservation!
- ▶ 5 years 6 months treatment with Leuprolide 11.25 mg monthly
  - By 4 months s/p start of tx, PE is stable
  - Stimulated LH shows suppression!
- ▶ 6 years 4 months treatment switched to Leuprolide 11.25 mg 3 month depot
  - 15 months later bone age has progressed by 12 months
  - Stimulated LH remains suppressed at 0.796 mIU/ml after 2<sup>nd</sup> injection

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Case Study: Peter  
Clinical Presentation



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Case Study: Peter  
Clinical Presentation



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Case Study: Peter  
Evaluation

- ▶ Gonadotropins
  - ICMA LH and ICMA FSH pubertal
  - Stimulation testing not needed
- ▶ Testosterone in pubertal range
- ▶ Bone age advanced by 3 years 6 months
- ▶ MRI of the pituitary gland revealed a hamartoma

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## Case Study: Peter Treatment

- ▶ Peter successfully treated with Lupron monthly

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## Potential Reasons to Treat with a GnRH Agonist

- ▶ Compromised Adult Height
- ▶ Psychosocial and Behavioral

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## So What's the Dilemma?

- ▶ Treatment for CPP is not always so clear cut
  - Will this treatment (with a GnRH agonist) make my child taller?
  - What is the best length of treatment with a single Supprelin implant?
  - Other potential dilemmas?

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## Will This Treatment (with a GnRH agonist) Make My Child Taller?

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## Case Study: Nicole Clinical Presentation

- ▶ Nicole is a 7 years 6 months old female with precocious puberty
- ▶ Parents report breast development within the past 6 months
- ▶ Family history is positive for CPP – mom was 9 years 6 months old at menarche

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### Case Study: Nicole Evaluation

- ▶ Baseline LH is 0.4 with estradiol of 3 pg/ml
- ▶ Height is at the 5<sup>th</sup> percentile
- ▶ Bone age advanced by about 18 months and predicts final height of 59"
- ▶ Mid-Parental Height (MPH) is 61"

**Will treatment make Nicole taller?**

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### Consensus Statement on the Use of Gonadotropin-Releasing Hormone Agonists in Children (2009)

- ▶ Greatest height gain in girls <6 years
  - 9-12 cm
- ▶ Girls between 6 and 8 years MAY have a moderate benefit
  - 4.5 +/- 5.8 to 7.2 +/- 5.3 cm
  - Therapy should be individualized
- ▶ Insufficient data in boys
  - Consider in all boys before 9 years

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### A Further Look at the Research...

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► Dutch Experience

- Height gain was 11.7cm, 7.9cm, and 6.1cm, respectively for < 6 years, 6-8 years and > 8 years

Mul, D., Oostdijk, W., Otten, B. J., Rouwe, C., Jansen, M., Delemare-van de Waal, H. A., ... Drop, S. L. (2000). Final height after gonadotropin releasing agonist treatment for central precocious puberty: The Dutch experience. *Journal of Pediatric Endocrinology Metabolism*, 13 (Suppl 1), 765-72.

► German Experience

- Height gain of  $5.5 \pm 1.4$  cm for entire group
  - Height gain in Group 1 (< 6 years) was significantly higher than Group 2 ( $9.5 \pm 2.3$ cm vs  $1.6 \pm 1.0$ cm)

Partsch, C. J., Heger, S., & Sippell, W. G. (2000). Treatment of central precocious puberty: Lessons from a 15 years prospective trial. German Decapeptyl Study Group. *Journal of Pediatric Endocrinology Metabolism*, 13 Suppl 1, 747-58.

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► NIH Experience

- For 6-8 years of age, average adult height was  $6.8 \pm 6.9$ cm greater than pretreatment predicted height
- Over half (48 of 91) of children came within 5cm of target heights
- **Careful evaluation of girls between 6-8 years of age – tempo!**

Klein, K. O., Barnes, K. M., Jones, J. V., Feuille, P. P., & Cutler, G. B. (2001). Increased final height in precocious puberty after long-term treatment with LHRH agonists: The National Institutes of Health Experience. *The Journal of Clinical Endocrinology and Metabolism*, 86, 4711-4716.

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## The Research Continues and So Do the Similar Findings

► Research Studies

- Carel, J. C., Eugster, E. A., Rogol, A., Ghizzoni, L., Palmert, M. R., Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology, ... Wit, J. M. (2009).
- Lazar, L., Padoa, A., & Phillip, M. (2007).
- Lee, P. A., Neely, E. K., Fuqua, J., Yang, D., Lois, M. L., & Mattia-Goldberg, C. (2011).

► Similar findings

- Modest height gain (4.5 -7.2 cm) for 6 – 8 year old females
- Treatment in kids 6-8 years old might not be warranted

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Case Study:  
Will Treatment Make Nicole  
Taller?

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Factors to Consider for Treatment

- ▶ Chronologic age
- ▶ Starting bone age
- ▶ Starting height
- ▶ Age of puberty
- ▶ Tempo of puberty
- ▶ Duration of potential treatment

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What is the Best Length of  
Treatment with a Single  
Supprelin Implant?

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## Supprelin Implant

- ▶ FDA approved for 12 months
- ▶ Dosing
  - 50 mg implant
  - Supprelin (histrelin) diffuses at average rate of 65 ug/day
  - So, in theory, implant provides enough medication for 2 years!



Egster, E. A., Clarke, W., Kletter, G. B., Lee, P. A., Neely, E. K., Reiter, E. O., ... Tierney, D. (2007). Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: A multicenter trial. *Journal of Clinical Endocrinology & Metabolism*, 92, 1697-1704.

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## Case Study: Addie Clinical Presentation

- ▶ 8 year 2 month old female with history of breast development beginning around 7 years 10 months by report
- ▶ Recent 5 inch growth spurt in the past year
- ▶ Bone age at CA of 8 years 2 months is advanced to 12 years of age
- ▶ Tanner 3 breast on exam

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## Case Study: Addie Evaluation

- ▶ Laboratory evaluation consistent with central puberty.

Study	Results
LH	0.609 mIU/ml
FSH	2.4 mIU/ml
Estradiol	1.9 pg/ml

- ▶ Adrenal labs and thyroid labs also normal.

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### Case Study: Addie Treatment

- ▶ Decision made to treat with GnRH agonist, Supprelin, for psychosocial reasons.
- ▶ Implant placed at 8 years 4 months of age.

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### Case Study: Addie Treatment

- ▶ 15 months s/p implant
  - Puberty exam stable
  - Growth velocity prepubertal
  - Bone age stayed stable after a year+ on treatment

	LH (mIU/ml)	Estradiol (pg/ml)
Baseline	0.609	1.9
7 weeks s/p implant	0.332	1.4
15 months s/p implant	0.088	1.3

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### What Would You Do?

- ▶ OPTION 1: Leave in longer
- ▶ OPTION 2: Remove and replace at 15 months
- ▶ OPTION 3: Remove and not replace

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### Case Study: Addie Treatment

- ▶ Supprelin replaced at 9 years 10 months, after 16.5 months.
- ▶ 4 months later (21 months total on treatment) at 10 years 2 months she was suppressed

	LH (mIU/ml)	Estradiol (pg/ml)
Baseline	0.609	1.9
7 weeks s/p implant	0.332	1.4
15 months s/p implant	0.088	1.3
4.5 months s/p 2 <sup>nd</sup> implant (total supprelin 20.5 m)	0.13	2.2

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### Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children (2009)

- ▶ “The 50 mg histrelin-acetate implant provides sustained suppression for 12 months.”
- ▶ No statement that addresses this controversy

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### A Single Histrelin Implant Is Effective for 2 years for Treatment of Central Precocious Puberty

- ▶ Prospective Study with 33 children with CPP
- ▶ Monitor at 6 month intervals
  - ICMA LH at 6 and 18 months
    - IF > 1 IU/L, then leuprolide stimulation test
  - Leuprolide stimulation test at 12 and 24 months
    - Suppression defined as LH ≤4 IU/L
- ▶ Bone age at baseline, 12 months and 24 months

Lewis, K. A., Goldyn, A. K., West, K. W., & Eagster, E. A. (2013). A single histrelin implant is effective for 2 years for treatment of central precocious puberty. *Journal of Pediatrics*, 163, 1214-1216.

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## A Single Histrelin Implant Is Effective for 2 years for Treatment of Central Precocious Puberty

(continued)

- ▶ Results
  - 29 patients completed the study
  - Peak LH at 12 and 24 months was equivalent
  - LH at 6 months and 18 months was pubertal for 17 and 14 patients, respectively
    - GnRH stimulation test confirmed complete HPG axis suppression in ALL cases!
  - Degree of skeletal maturation declined significantly over 24 months
  - Tanner staging improved or stabilized in vast majority of patients (2 did not finish study)
  - Difficulty with implant removal occurred in 12 cases (39%)
    - Implant breakage = 6 cases; Implant migration = 1 case; Need for perpendicular incision = 8

Lewis, K. A., Goldyn, A. K., West, K. W., & Eugster, E. A. (2013). A single histrelin implant is effective for 2 years for treatment of central precocious puberty. *Journal of Pediatrics*, 163, 1214-1216.

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## Experience with the Histrelin Implant in Pediatric Patients

- ▶ Review article
- ▶ Important advancement that histrelin implant is effective for 2 years based on 2013 study
- ▶ Safety
  - ▶ Implant breakage (22-39%) and difficulty with localization
    - ▶ Appear higher when left longer?

Eugster, E. A. (2016). Experience with the histrelin implant in pediatric patients. *Endocrine Development*, 30, 54-59.

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## An Observation ... Hmmm

- ▶ The Children's Hospital of Philadelphia (unpublished data)
  - ▶ Over 500 procedures
  - ▶ Adverse events based on recall: 1 removed for mood changes, 1 for infection and several needed perpendicular incision for breakage
  - ▶ Official chart review underway!

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## Advantages and Disadvantages with Longer Treatment

► Advantages

- Less procedures, potentially less sedation
- Reduce cost
- Excellent HPG axis suppression

► Disadvantages

- Difficulty monitoring suppression with a ICMA LH alone
  - Many of patients ICMA LH does not revert back to prepubertal range despite suppression
  - Disadvantage regardless of length of treatment
- *Surgical complications with implant removal*

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Should Addie Have Been Treated Longer With the Same Implant?

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And One Dilemma Leads to Another....

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## Should We Use Routine Lab Monitoring for Children with Supprelin Implant?

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### Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children (2009)

- ▶ Tanner stage and growth monitored every 3-6 months
- ▶ BA monitored periodically
- ▶ NO consensus about the routine use of random or stimulated measurements of gonadotropins or sex steroids for monitoring therapy

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### LH monitoring for Supprelin Specifically

- ▶ Recall from study above by Lewis et al. looking at Supprelin for 2 years, LH was often NOT prepubertal, BUT a GnRH stim test confirmed suppression in ALL cases!
- ▶ Multiple studies show that random LH often remains pubertal in children treated with the Histrelin implant

Lewis, K. A., & Eugster, E. A. (2013). Random luteinizing hormone often remains pubertal in children treated with the histrelin implant for central precocious puberty. *Journal of Pediatrics*, 162, 562-65.  
Neely, E. K., Silverman, L. A., Geffner, M. E., Danoff, T. M., Gould, E., & Thornton, P. (2013). Random unstimulated pediatric luteinizing hormone levels are not reliable in the assessment of pubertal suppression during histrelin implant therapy. *International Journal of Pediatric Endocrinology*, 1-5.

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One Dilemma Leads to Another...

....Should We Use Routine Lab  
Monitoring for Children with  
Supprelin Implant?

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And I Leave You With That  
Dilemma to Ponder!

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