The 12th annual Yale Pediatric update

- No disclosures
The fascinating mystery

What initiates puberty??

Gonadostat hypothesis

What is the “trigger”? 

Parent et al, Endocrine reviews, 2003
Multiple permissive signals

- Genetic programming (70%) 2.2, 12.0, 12.9, 18.6 months
- Environmental factors (30%)
- Key regulatory genes (Kisspeptin- GRP54 signaling)

“ON”
- GH/IGF-1
- Glutamate
- Leptin
- Obesity
- Skeletal maturation (10.75 yrs and 13 yrs)

“OFF”
- CRF/Cortisol
- GABA
- Neuropeptide Y
- Opiods
- Anorexia
- Excessive exercise
- Stress
Does puberty begin with a kiss??

Kisspeptin/GPR54 signaling

- KiSS-1 gene encodes kisspeptin
- Kisspeptin binds to GPR54 receptor and stimulates GnRH release
- Neuropeptides kisspeptin and neurokinin B are essential gatekeepers of puberty
KiSSpeptin stimulates GnRH release

Dungan et al: Endocrinology 2006

GnRH neurones

• Migrate with olfactory bulbs from nasal placode

• Remarkably less than 2000 in number

• Intrinsic pulsatility

• Pulsatile network of neurones “GnRH pulse generator”

• Higher frequency results in LH secretion
Normal Puberty Timing

- **Girls**
  - Height spurt: 9.5 to 14.5
  - Breast:
    - Stage 1: 8 to 13
    - Stage 2: 13 to 18
  - Pubic hair:
    - Stage 2: 2
    - Stage 3: 3
    - Stage 4: 4
  - Menarche: 10 to 16

- **Boys**
  - Height spurt: 10.5 to 16
  - Pubic hair:
    - Stage 2: 2
    - Stage 3: 3
    - Stage 4: 4
  - Testes:
    - Stage 1: 9.5 to 13.5
    - Stage 2: 13.5 to 17
  - Penis:
    - Stage 1: 10.5 to 14.5
    - Stage 2: 12.5 to 16.5

**LH Changes Independently of the Gonadal Feedbacks of the Ovary.** Therefore, only changes in the hypothalamic-pituitary complex are needed to bring about the pubertal rise in gonadal steroid hormones. (From: Ross, G. M. (1981). *Pediatric Neuroendocrinology.* S. Karger, New York.)
Linear Growth in Puberty: Girls

- Slight deceleration just before puberty
- Acceleration begins at B2 (estrogen, augments GH secretion)
- Peak height velocity of 8.25 cm/yr at B3 (~1yr prior to menarche)
- Post menarche additional 7.4 cm (2-3 inches) of growth reserve
- 10 cm if early menarche (10 yrs), 5 cm delayed menarche
- Growth ~ 99% complete by BA of 15 yrs
- Up to 50% of cycles are anovulatory in the first 2 yrs post menarche

Linear Growth in Puberty: Boys

- Pubertal growth spurt on average 2 yrs later than girls
- Peak height velocity of 9.5 cm/yr at G3 to G4
- Spermache G3 to G4, facial hair and voice changes G4
- Growth ~ 99% complete by BA of 17 yrs
- Longer pre-pubertal growth and greater peak height velocity is responsible for height discrepancy between males and females
Tanner staging

- Based on 1969 photographs of 192 institutionalized white British girls
- Low socioeconomic class, not representative of the British population

Central Precocious Puberty: Definition

- When is puberty Precocious?
- Traditionally, Tanner stage B2 and G2 before age 8 yrs in girls and 9 yrs in boys
Pediatric Research in Office Setting network (PROS) study

- 1992-1993, 17077 girls between 3 yrs and 12 yrs examined
- Breast and pubic hair developed ~ 1yr earlier in whites (10 yrs) and 2 yrs earlier in blacks (8.9 yrs)
- Menarche mean age (12.9 yrs) in whites (12.2 yrs) in blacks

Herman-Giddens et al, Pediatrics 1997

LWPES changes guidelines

- New guidelines for definition of precocious puberty proposed in 1999 (girls only)
- Evaluation if breast or pubic hair occurring before age 7 in whites and before age 6 in blacks

Kaplowitz et al, Pediatrics 1999
Opposing view

Vigorous opposition

- Premature conclusions based on flawed study
- Liberalization of “normal” carries risk of overlooking pathology
- Agreement that slow tempo to menarche
- Warrant at minimum clinical, height and bone age evaluation if < 8yrs regardless of race (8%, 34%)

Rosenfield et al. Pediatrics, 2000
Limitations

- Examination by visual inspection
- Multiple observers
- Patients not randomly selected from general population
- “Hidden agenda” visits
- Data not corrected for racial representation (only 10% African American)

Breast Cancer and the Environment Research Program Study (BCERP)

- BCERP puberty arm, investigating environmental exposures and onset of puberty
- Longitudinal study of 1239 girls enrolled between 2004-2008 at 6 years to 8 years, followed longitudinally 2004-2011 (San Francisco Bay area, Greater Cincinnati, New York City)

Breast Cancer and the Environment Research Program Study (BCERP)

- Age at onset of B2 varied by race/ethnicity and BMI at baseline

- Median age at B2 was 8.8 for Black, 9.3 for Hispanic, 9.7 for White and 9.7 years for Asian participants

- At 8 years, 43% Black, 31% Hispanic and 18% White girls were >B2

Breast Cancer and the Environment Research Program Study (BCERP)

- Higher BMI was the strongest predictor of earlier age at B2
  [BMI 14.2% variance, race 4.4% variance (race/ethnicity remained significant in adjusted models)]

- Girls in all BMI categories >50% were progressively more likely to reach B2 compared to girls <50%

- Percentage of BCERP girls with BMI > 85th % included, 39% (17%) Black, 44% Hispanic, 26% (19%) White and 12% Asian girls
Conclusions

- Age of B2 was earlier in White (4 months) but not Black girls compared to PROS Study

- Obesity epidemic “prime driver” of earlier onset of puberty in BCERP study but did not account for all

- Although overall age of breast development onset for BCERC black girls was not different from PROS girls, their proportion of African American first-graders at Tanner 2 tripled in the 15 years between the studies
  - 12 months earlier in Danish girls over 15 years

Comparing the cumulative prevalence of Breast Stage 2+ for non-Hispanic white participants between the BCERP Puberty Study and PROS


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Menarche: Secular Trends

Sorensen, Hormone Research in Peadiatrics 2012
Menarche: Secular Trends

- In a cohort of 104, US children referred for evaluation of early puberty
- Premature Adrenarch 46%
- Premature Thelarche 18%
- Central Precocious Puberty 9% (of which only half had progressive disease that required treatment)
- Pubic Hair of infancy 8%
- Premature menses 5%
Results: Diagnostic Classification

- Insufficient data (n=42, 16%)
- Premature adrenarche: (n=98, 36%)
  - Premature adrenarche: (n=98, 36%)
  - Prepubertal (n=30, 11%)
- Brain pathology: (n=26, 9%)
- Peripheral precocious puberty: (n=7, 3%)
- Late onset CAH (n=2, 1%)

Benign Premature Thelarche

- Isolated breast development (absence of pubic hair, growth acceleration or advanced bone age)
- Onset within the first 3 years of life
- Transient/partial activation of hypothalamic-pituitary-ovarian axis with predominant FSH secretion
- Need to exclude CPP/ exposures (lavender, tea tree oil)
- Progression to CPP in ~ 14%
Premature Thelarche: Prevalence/natural history

- Among an unselected population of girls in the US aged 12-48 months, the prevalence of Premature Thelarche was 4.7% (15 of 318)
- Peak prevalence was between 12-17 months
- At follow up (> 6 months) PT still present in 44%

Curfman et al: Journal of Pediatric & Adolescent Gynecology

Premature Thelarche: Clinical Course

- Follow up of 139 girls with PT from 1995-2005,
- PT regressed in 51%, persisted in 36%, cyclic course in 10% and progressed in 3.2%
- A progressive or cyclic course was more prevalent among girls presenting after 2 years of age
- CPP occurred in 13% regardless of age at presentation
- Mean age at menarche 11.9 yrs significantly younger than maternal menarche of 13.2 yrs
- No association with Soy exposure
- No association with Prematurity or SGA

Premature Adrenarche

- Slowly progressive pubic or axillary hair, body odor, acne
- Not accompanied by breast development or testicular enlargement
- Often mild bone age advancement and growth acceleration
- Risk factors include obesity, SGA, Prematurity
- Due to idiopathic early maturation of zona reticularis
- Modest DHEA-S elevation in early pubertal range
- Adult height not compromised and puberty in early normal range
- However can be first sign of CPP
- May be precursor to PCOS/metabolic syndrome
Pubic Hair of infancy

- Atypical variant of Premature Adrenarche?
- Retrospective chart review of infants <12 months
- Eleven identified (6 male)
- Average age 5 months; clinical diagnosis 8 months
- Majority (73%) had pubic hair in atypical location (scrotal in all boys)
- Growth, labs, BA were unremarkable
- Pubic Hair resolved by 11 months
- Appears to be benign entity but prudent to follow with minimal hormonal testing

Nebesio and Eugster: Pediatrics 2006

Mini Puberty

- Gonadotropin inhibition discontinues with placental separation, the hypothalamo-pituitary-gonadal axis is activated

- Boys: LH (x 10 cord blood) and Testosterone peak in first 24 hrs after birth with dramatic fall in first week of life followed by second peak at 2 months of age and nadir at 6 months (LH, Testosterone, FSH, InhibinB)

- Girls: No LH peak at birth, later (3-6 months) and more sustained LH and FSH (2-3 yrs) elevation in infancy

- LH concentrations greater in boys, FSH higher in girls

- Role in future spermatogenesis and fertility (2-fold increase in testicular size from birth to 5 months, then unchanged till 2 yrs)

- Mini puberty absent in AIS (lack hypothalamic AR expression, hence resistant to feedback)
Precocious Puberty: Considerations

- Age
- Sex (10 times as common in girls)
- Race
- Central/peripheral
- Underlying CNS, gonadal, adrenal tumor
- Final height
- Psychological implications

Causes of precocious puberty

**Central precocious puberty**
- Idiopathic
- International adoption

**CNS aberrations**
- Hypothalamic hamartoma (congenital)
- Astrocytoma and glioma
- Cerebral palsy
- Hydrocephalus
- Irradiation
- Trauma
- Infection
- Subarachnoid cyst
- Pineal cyst
- Neurofibromatosis type 1
- Tuberous sclerosis
- Sturge–Weber syndrome

**Gn-independent PP** (feminization)
- Functional ovarian cysts
- McCune–Albright syndrome
- Ovarian tumor (granulosa cell)
- Exogenous estrogen
- Profound primary hypothyroidism
Environmental Factors

- Endocrine disruptors
- Intrauterine (IUGR)
- Adoption (precocious puberty in immigrant kids)
- Single parenting/stress

Precocious Puberty: Who to treat?

- Rapid progression (BA > 2 yrs advanced)
- PH of > 2 SD below MPH
- PH < 150 cm or 59 inches
- CNS symptoms
- Significant psychological concerns

LWPES, Pediatrics 1999
Precocious Puberty

• Should 6-8 yr old girls be routinely treated?

• How about 7-8 yr old girls??

• Why treat?

“She will end up short”

• Most have a slowly progressive variant and do not show loss of predicted height if followed without treatment

• Post menarche height gains of 7.4 cm on average, but 10 cm in early menarche (10yrs), 5 cm delayed menarche
Height: is GnRHa therapy Beneficial?

• Data pooled from 10 studies (131 treated and 66 untreated CPP girls)

• < 6 yrs (160.4 cm vs. 153.9 cm)

• > 6 yrs (157.5 cm vs. 157 cm)

Kletter et al, JCEM 1994

She is 7 years will she have a period soon?

• Slower tempo to menarche (2.8 yrs vs. 1.4 yrs) and more growth reserve after menarche

Edward Munch 1893
How about psychological considerations?

• Difficult to study
• Paucity of well designed studies
• Conflicting results

Behavioral Problems

• Psychological studies have shown that girls entering puberty earlier than normal are vulnerable to behavioral problems

• However no studies of shown that intervention with GnRHa affects these outcomes or quality of life
Swedish Experience

- Prospective study of 51,466 women
- Interviewed at ages, 10 yr, 13 yr, 15 yr, 25 and 43 yrs
- Early maturing (menarche < 11 yrs) compared to (menarche > 11 yrs)

Ritzen et al Endocrine Dev 2005

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Swedish experience

- No differences at baseline (10 yrs)
- At ages 13 and 15 yrs, higher incidence of drug/alcohol abuse, shop-lifting, truancy, earlier sexual debut (abortion rate 14% vs. 5%) in early maturing
- At 25 and 43 yrs both groups were well adjusted socially, no difference in criminality, drug abuse or smoking
- However early maturing group had lower educational and employment status and married men with lower educational status

Ritzen et al Endocrine Dev 2005
Precocious Puberty: Evaluation

| Pediatrician | • Family and personal history  
| • Chart growth velocity/history*  
| • Assess physical signs of puberty  
| • Assess for underlying pathology  

| Pediatrician or Endocrinologist | • Bone Age  
| • Determine predicted adult height  
| • Sex Hormone evaluation  
| • Pelvic ultrasound  
| • Order MRI if indicated  

| Endocrinologist | • GnRHa stimulation test  
| • Candidacy for GnRHa therapy  
| • Order MRI  
| • Initiate GnRHa therapy  
| • Monitor response to therapy  

MRI (who to image)

- All boys (high prevalence of CNS lesions 40%)
- All girls with rapidly progressive puberty
- Girls < 6 yrs (higher yield 6-33%)
- Girls 6-8 yrs (much lower yield 2%)
British Study 1990-2001

- 67 girls with CPP*
- Mean age at diagnosis 6.2 yrs (2 – 7.9 yrs)
- Intracranial pathology in 10 (15%)
- 6 (60%) hypothalamic harmatomas
- No statistical difference between MR+ and MR- group with respect to age, pubertal stage, BA, pelvic USS, HT and BMI SDS, LH/FSH ratio

Ng et al, Arch Dis Child 2003

The MRI findings

Ng et al, Arch Dis Child 2003
Pelvic Ultrasonography in the evaluation of CPP

- Sonographic evidence of CPP include
- Ovarian volume of ≥ 2ml (largest, smallest, or average)
- Uterine volume of ≥ 4ml
- Uterine length of ≥ 4ml
- Pubertal configuration of uterus with a thickened endometrial stripe of ≥ 0.2ml

Utility of US in CPP diagnosis

- In the challenging cohort of girls with clinical finding but pre-pubertal random LH
- Studies comparing stimulated LH with US findings have been conflicting
- The significant variability and overlap in ovarian and uterine volumes does not allow for accurate separation
- Contrary to leuprolide stimulation, pelvic US alone cannot distinguish between pre-pubertal and pubertal females

Sathasivum and Rapaport: Journal of Pediatrics 2011
## Precocious Puberty: Treatment

<table>
<thead>
<tr>
<th></th>
<th>1-Monthly Depot</th>
<th>3-monthly Depot</th>
<th>12-monthly implant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td>Leuprolide</td>
<td>Leuprolide</td>
<td>Histrelin</td>
</tr>
<tr>
<td><strong>Brand name</strong></td>
<td>Lupron depot-PED-1</td>
<td>Lupron depot-PED-3</td>
<td>Supprelin LA</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Every 28 days (3.75 mg, 7.5 mg, 15 mg)</td>
<td>Every 90 days (11.25 mg, 30 mg)</td>
<td>Every 1 year</td>
</tr>
<tr>
<td><strong>Advantage</strong></td>
<td>Efficacy, well studied</td>
<td>Fewer injections Few compliance issues</td>
<td>No injections Potent suppression</td>
</tr>
<tr>
<td><strong>Disadvantage</strong></td>
<td>Painful injections</td>
<td>Painful injections</td>
<td>Cost, minor surgical procedure, may require anesthesia</td>
</tr>
<tr>
<td><strong>Side effect</strong></td>
<td>Sterile abscess</td>
<td>Sterile abscess</td>
<td>Implant site reactions, potential scarring</td>
</tr>
</tbody>
</table>

### Sequential Comparisons of One-Month and Three-Month Depot Leuprolide Regimens in Central Precocious Puberty

*Badaru, Neely JCEM 2006*
Histrelin: Limited long-term follow-up

- Greater suppression of HPA axis compared to depot GnRHα

- Also more rapid recovery once implant removed (LH, FSH increase within 3 weeks compared to 3 to 4 months)

- Because low levels of estrogen are needed for IGF-1 generation, over suppression may be detrimental to final height

Depot 3 - month 11.25mg $5037.19/$25-50 deductible for most insurances/$10.00 co-pay with coupon

Depot 1-month 7.5mg $1040.00/$25-50

Histrelin implant - $20,000.00 minus Hospital fees