Controversies in Precocious Puberty!!!

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Disclosure

• I have no financial relationships with any commercial interests related to the content of this activity today.

Learning Objectives

• To understand the dynamic influences in the onset of puberty
• To recognize the clinical features of precocious puberty
• To understand the health implications of altered pubertal timing

Neural and Hormonal Control of Pubertal Development

Independent but temporally linked to pubertal process

Hypothalamus → Gonadarche → Adrenarche

KISSPEPTIN PATHWAY

**KISSPEPTIN GENE**
- Kisspeptin is a 54 aa protein encoded by KISS1 gene located on Chr 1
- Ligand for KISS1R (GPR54), G-protein coupled
- Transcribed in the brain, adrenal gland, and pancreas

**Functions:**
- Metastasis suppressor gene in Melanoma and Breast cancer
- Initiate secretion of GnRH at puberty

**Phenotype:**
- Lack of pubertal development
- Low sex steroid
- Low gonadotropin levels
- Sterility
- CPP – delayed degradation or persistence in the ligand-receptor complex


**Mean Age of onset of breast development**
- Whites – 9.96 yrs
- African Americans – 8.87 yrs

**NHES – 1966 – 1970**
- Whites – 10.38 yrs
- AA – 9.48 yrs

1997, 17,000 girls aged 3-12 yrs in the US

***Defined precocious puberty as development before age 8 years
8% of white and 25% of black girls exhibited precocious sexual development***

Marcia E. Herman-Giddens et al. Pediatrics 2012;130:e1058-e1068
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**Secondary Sexual Characteristics in Boys: Data from the Pediatric Research in Office Settings Network**

**Table 1**

<table>
<thead>
<tr>
<th>Race</th>
<th>Age (Yrs)</th>
<th>Percentage with breast development</th>
<th>Percentage with pubic hair</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PROS (%)</td>
<td>NHANES III (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>White</td>
<td>7</td>
<td>5.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Black</td>
<td>7</td>
<td>15.4</td>
<td>23.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7</td>
<td>14.9</td>
<td>14.9</td>
</tr>
<tr>
<td>White</td>
<td>8</td>
<td>10.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Black</td>
<td>8</td>
<td>37.6</td>
<td>27.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8</td>
<td>25.4</td>
<td>30.9</td>
</tr>
</tbody>
</table>

Kaplowitz, P. Advances in Pediatrics 58 (2011) 243-258
### Mean Ages +SD (years) for Menarche

<table>
<thead>
<tr>
<th>Year</th>
<th>Menarche</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall and Tanner (UK) 1969</td>
<td>13.47±1.02</td>
</tr>
<tr>
<td>PROS 1992-1993</td>
<td>Whites – 12.88±1.2 AA – 12.16±1.21</td>
</tr>
<tr>
<td>Bogalusa Heart Study 1973-1994</td>
<td>Advance of 9.5 mos for AA, 2 mos Whites</td>
</tr>
</tbody>
</table>

NHANES III – 8-16 yrs
Slyper A, Clin Endocrinol 2006; 65:1-8

### Social Reasons for Concern with Declining Age of Puberty

- Childhood from physiologic development
  - Pressures, more anxiety, negative self images and suicide attempts
  - Engage in risky behaviour - more likely to abuse drugs, take up cigarette smoking and drink alcohol
- Receiving end of physical and sexual violence
- Lower level of academic achievement
- Higher and earlier level of sexual activity, likely to have a teenage pregnancy
- Early maturing boys do not have these same behavioural patterns

Sandra Steingraber “The Falling Age of Puberty in US Girls” 2007

### Medical concerns for Early Puberty in Girls

- Increased risk for breast cancer in adulthood
- Exposure to EDCs during childhood is associated with breast and testicular cancers
- Emotionally and psychologically unequipped to handle puberty

### Implications of Altered Puberty Timing

- Risk for short adult height
- Engage in risky behavior such as early sexual encounters, drug abuse
- Potential sexual abuse
- Psychosocial difficulties
- Concern for the development of reproductive tract cancers later in life
  - Early menarche is a risk factor for breast cancer – extended lifetime exposure to estrogen
  - Testicular cancer

Multiple sources

### Age-adjusted incidence of testicular cancer related to activity of selected hormones.

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### Timing of Menarche - International

- Europe – 1830, ave age 17 yrs (3)
- US – 1900. ave age 14.2 yrs
- US – 1920s, ave age at menarche – 13.3 yrs
- Rural China – 1980s menarche 17 yrs
- Ireland - 1986 – 13.52
- Ireland - 2006 -12.53 (7)

1. Biro FM et I Pediatrics 2010

### Implications of Altered Puberty

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Multiple sources
Permissive Factors in the Earlier Onset of Puberty

- Excess Adipose Tissue (Obesity)
  "Adipose Tissue as an Endocrine Organ"

Kershaw, EE and Flier Jeffrey S.
JCEM 89:2548-2556, 2004

Endocrine-Disrupting Chemicals (EDC)

- Synthetic chemicals that mimic, inhibit, or alter the action of natural hormones. Break down slowly and accumulate in fatty tissues of animals.
  - Organochlorine pesticides 21, DDT and endosulfan
  - Plastics
  - Fuels
- Chemicals
  - BPA – manufacture of lycarboante plastics such as rigid cups, water bottles, food storage containers, linings of food cans, dental sealants (leach during heating and washing).

Environmental Exposure to Sex Steroids

Past 10 years – modest number of case reports or series; thru skin contact
- Topical Androgens – Androgel
- Topical Estrogen cream – Premarin
- Topical Estrogen patch

Clinical features: Rapid genital enlargement with pubic hair or breast enlargement
- Biochemical feature:
  - elevated levels of Testosterone or Estradiol
  - Prepubertal LH and FSH

Definition of Central Precocious Puberty (CPP)

- Definition:
  - Premature reactivation of the HPG axis before age 9 yrs in boys and 8 yrs in girls, or menarche before age 9 yrs with accelerated growth and biologic or bone maturation
- Epidemiology:
  - US incidence: 1:5000 to 1:10,000
  - Female predominance, F:M from 3.1 to 23.1

Specific Genes Linked to CPP

- **KISS1R Gene**
- **MKRN3 gene**
  - *FSH-b and LH-b*expressed in the hypothalamic arcuate nucleus.
  - decreased expression
    i. upregulation of the KISS1 gene.
    ii. Increased GnRH pulses
- **Neuropeptide Y subtype**
  - NPY – thought to be an inhibitor of GnRH secretion
- **LIN28**

**Study findings are intriguing and contradictory, and no clinically significant mutation have yet been observed that cause a functional deficit at a molecular level – 2015**
Etiology of CPP

- Girls
  - 75% to 85% - idiopathic
  - 27.5% - genetic basis, AD with incomplete penetrance
  - <4 yrs of age: CNS lesions are common
- Boys
  - More likely to have pathological source
  - 50% with progressive CPP


Risk Factors for CPP

- International adoption
- Congenital and acquired CNS insults
  - Septo-optic dysplasia
  - Hypothalamic Hamartoma
  - CNS tumor
  - Traumatic brain injury
  - CNS infection
  - CNS ischemia
- Genetic syndromes
  - NF-1
  - Sturge-Weber Syndrome
  - Tuberous Sclerosis
- Low dose radiation
- Hydrocephalus

Should all girls with CPP require a Pituitary MRI?

- Study from Paris
  - 19% - abnormal brain imaging, if onset of CPP before age 6 yrs
  - 2% - if onset of CPP between ages 6 and 8 yrs
- US endocrinologists
  - Between 6- to 8-year-olds – not routinely
- European endocrinologists – more likely to do Brain MRI
- Consensus Guidelines for the use of GnRH analogs in Children, LWPEES and ESPE recommend Pituitary MRI ....
  - All boys with CPP
  - Girls with onset before age 6 yrs, +neurologic findings i.e. headaches; very rapid progression

Reasons to Treat CPP

☑ Primary goal: Preserve final adult height
  - Greatest gain in height – girls with onset of puberty before age 6 yrs
  - Girls with onset between 6 and 8 yrs, may still benefit from treatment
  - >8 yrs – no benefit from intervention, therefore treatment is not indicated.
  - Benefit in males – limited
☐ No consensus whether CPP is associated with psychological distress and whether treatment ameliorates these problems

Consensus Guidelines for the use of GnRH analogs in Children
November 2007. LWPEES and ESPE.
Published in Pediatrics 2009

Treatment for CPP - GnRH Agonist

- Children with progressive pubertal development
- Accelerated growth over 3- to 6-month period
- Girl is already Tanner 3 or greater for breast development
- Most compelling reason: prevent compromise of adult stature
- Girls with developmental delay and have difficulty with pubertal development

- Mechanism of Action:
  - Desensitize gonadotroph response to GnRH pulses by continuous exposure
- Depot preparation
  - Lupron monthly
    - 7.5 mg dose; $9500 per year
    - 11.25 mg; $18,000 per year
  - 3-monthly dosing
- Histrelin Implant (SUPPRELIN LA) – continuous diffusion from the implant through microporous walls
Resumption of Puberty in “Girls” Following Removal of Histrelin Implant

Treated n = 30 girls
Average age of menarche = 12.94, similar to general population
Treated with no menarche yet = 4, time from explantation = 12.36 yrs

Resumption of Puberty in “Boys” Following Removal of Histrelin Implant

**All demonstrated increase in testicular volume within 1 year after Histrelin explantation**

Long-Term Continuous Suppression With Histrelin Implant for CPP: Final Report of a Phase 3 Multicenter Trial

• Design: Phase 3, prospective, open-labeled study
• Participants: 36 children
• Length: 4 yrs
• Results:
  — Hormonal suppression maintained throughout study
  — BA to CA – decreased, 1.417 to 1.18
  — PAH: Girls increased 151.9 to 166.5 cm (gain 10.7 cm)

Silverman LA et al, J Clin Endocrinol Metab. 2015 Jun; 100(6): 2354–2363.

Long-Term Continuous Suppression With Histrelin Implant for CPP: Final Report of a Phase 3 Multicenter Trial

• Adverse Events
  — Implant site reactions, i.e. pain or discomfort
  — Aching, soreness, irritation, redness, swelling, scarring, keloids
  — Extrusion of suture
  — Implant breakage 22.1%
  — Surgical difficulty – encapsulation of implant or presence of scar tissue
  — Depression and aggression
  — Weight gain

Silverman LA et al, J Clin Endocrinol Metab. 2015 Jun; 100(6): 2354–2363.

Conclusion

• The younger age at puberty appears to be part of a natural process
• Environmental factors appear to accelerate the trend
• Children’s hormonal systems are being altered and early puberty is the coincidental, non-adaptive outcome
• Secular trends in puberty timing can be associated with many health consequences such as endocrine-related cancer and metabolic syndrome
• Early puberty may bring psychosocial disturbances
• Treatment for central precocious puberty is effective and has no long-term sequelae

Thank You
**Premature Thelarche in Infants and Toddlers**

- Van Winter et al (Olmsted County, Minnesota, 1940 to 1984)
  - Aged 2-8 yrs
  - 0.6 per 1000 person yrs
  - Highest in the 1st yr of life, decreases until the 5th when it rises again

- Curfman AL et al 2009 (age 12-48 mos)
  - Prevalence: 4.7%
  - Whites – 4.2%
  - Blacks – 4.6%
  - White Hisp – 6.5%

- Herman-Giddens et al, (1997) n = 17,077, ages 3-12 yrs
  - Prevalence in 3-4 yrs old:
    - Whites – 0.7%
    - Blacks 2.1-2.8%

**Clinical features of Premature Thelarche**

- Isolated appearance
- Younger than 3 yrs old
- No associated growth spurt
- Bone age is normal
- Behaviour is age-appropriate
- Self-limiting

**Estradiol level in premature thelarche vs normal prepubertal girls.**

- The bars are mean ± SD
- *P < .01 versus normal.

**Long-term sequelae of premature thelarche**

- **Favorable sequelae**
  - Spontaneous regression
  - No psychological sequelae
  - No effect on actual onset of puberty and no effect on fertility??? No good evidence for this. Area for research
  - Final stature is unaffected

- **Adverse events**
  - Progression to central PP
  - Tendency for isolated cyst formation
  - Early exposure to estrogen as in central PP have higher incidence of breast cancer??? Area for research

**Premature Adrenarche**

- **Characteristics:**
  - F>M 10:1
  - No penile or clitoral enlargement
  - Breast remains prepubertal
  - Tempo of puberty is normal
  - Slight bone age advancement
  - Distinguish this from late-onset CAH (17-OHProgestrone level after ACTH stimulation)

- **Tests:**
  - DHEAS, 17-OHProgestrone
  - Bone age – can be slightly advanced
  - Adrenal ultrasound

**Possible explanation for Premature Adrenarche**

- Elevated sex steroids i.e. DHEA and DHEAS, Δ4, and testosterone (New et al JCEM 42:117 and Forest JCEM 43:982)
- Abnormal regulation of androgen-forming enzyme within the ovary
- Increased cytochrome P450C17 activity in both the adrenals and ovaries
- Increased peripheral sensitivity to androgens; familial trait linked to dominant non-HLA linkage
Risk factors for premature adrenarche

- Low birth weight
- Obesity

Sequeleas of Premature Adrenarche

- Functional ovarian hyperandrogenism (PCOS)
- Hirsutism
- ± Insulin resistance
- Dyslipidemia
- Functional ovulatory dysfunction (oligomenorrhea)