Handouts

GROWTH CHART REVIEW
Exogenous obesity

IBD

Primary Hypothyroidism

Van Wyk-Grumbach Syndrome

Intracranial mass

Or GH deficiency

Or Hypothyroidism
### Boys, 2 to 20 years

#### STATURE FOR AGE AND WEIGHT FC

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Stature (cm)</th>
<th>Weight (kg)</th>
<th>BMI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>110</td>
<td>16</td>
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<tr>
<td>3</td>
<td>115</td>
<td>18</td>
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<tr>
<td>20</td>
<td>200</td>
<td>52</td>
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</tr>
</tbody>
</table>

*To Calculate BMI: Weight (kg) = Stature (cm) x Stature (cm) x 10,000

<table>
<thead>
<tr>
<th>AGE (YEARS)</th>
<th>WEIGHT</th>
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<td>2</td>
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<tr>
<td>3</td>
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<td>75</td>
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<td>18</td>
<td>80</td>
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<tr>
<td>19</td>
<td>85</td>
</tr>
<tr>
<td>20</td>
<td>90</td>
</tr>
</tbody>
</table>

Source: Developed by the National Center for Health Statistics in cooperation with the National Center for Chronic Disease Prevention and Health Promotion (2000). Additional copies are available for purchase in quantities of 100. For order contact: American Academy of Pediatrics.
Hypothyroidism
Van Wyk-Grumbach syndrome
Intracranial mass
or
GH deficiency
Or
Hypothyroidism
Familial short stature
Constitutional delay of growth and puberty (CDGP)
Turner syndrome
CDGP AND TURNER SYNDROME

- Back to the delayed puberty
ROADMAP

• Definitions
• Clinical findings
• Precocity
• Link between puberty and growth
  • Growth chart review
• Delay
• Back to puberty and it’s mechanisms
• Perturbations to normal timing
  • Is it happening earlier? Why?
• When to refer
IS THE AGE OF PUBERTY TRENDING YOUNGER?
• Pediatric office visits 1992-1993
• 18,549 girls in study

Secondary Sexual Characteristics and Menses in Young Girls Seen in Office Practice: A Study from the Pediatric Research in Office Settings Network
Marcia E. Herman-Giddens, Eric J. Slora, Richard C. Wasserman, Carlos J. Bourdony, Manju V. Bhapkar, Gary G. Koch and Cynthia M. Hasemeier
Pediatrics 1997;99:505
DOI: 10.1542/peds.99.4.505
CONCLUSION

• Girls across the US are developing pubertal characteristics at younger ages
• Revise criteria for referral of girls for precocious puberty
POSSIBLE PROBLEMS WITH THE STUDY

- Visual inspection of pubertal changes as opposed to palpation
-Used Breast and/or pubic hair
-Visits were for HCM but also sick visits warranting full exam like abdominal pain
-No mention of BMI
-Concern that if the age is lowered, some real pathology may be missed
FINDINGS

• By age 7y breast and/or pubic hair development in 27.2% of AA girls and 6.7% of W girls
• By age 8y breast and/or pubic hair development in 48.3% of AA girls and 14.7% of W girls
• At any age and for any characteristic AA more advanced
• Mean age onset breast 8.87y AA and 9.96y W
  Mean age onset PH 8.78y AA and 10.51y W
  Mean age menarche 12.16 AA and 12.88 W
BIRO, ET AL. *PEDIATRICS* 2010

- **Inspection** and palpation used, BMI
- 1239 girls, 3 centers, 2004-2006
- Findings
  - By age 7y breast >= Tanner II development in 23.4% of AA girls and 10.4% of W girls and 14.9% H girls
  - By age 8y breast >= Tanner II development in 42.9% of AA girls and 18.3% of W girls and 30.9% H girls
  - Concluded that the proportion of girls with breast development at 7 or 8 years is greater than girls born 10-30 years earlier
ROSENFIELD, ET AL.  
*PEDIATRICS* 2009

- To answer the NHANES III reports about the earlier development
- If *obesity* is the culprit, need to know prevalence of early puberty in non overweight.
- Attainment of Tanner II breast in **NON OBESE** females
- Attainment of Tanner **III PH (not II)**
- Attainment of Menarche
- Compared all to obese children
ROSENFIELD, ET AL.
PEDIATRICS 2009

- **Normative data** for thelarche, pubarche and menarche in non-obese US children
- In the general population of non-obese children
  - Breasts and pubic hair in girls *(inspection)* are unusual < 8 years
  - Pubarche is unusual in boys < 10 years
- **Adiposity** and *ethnicity* are independently associated with earlier pubertal development
ROSENFIELD, ET AL.

PEDIATRICS 2009

• Obesity confounds pubertal start
  • Not only due to confusing (inspection-based studies) fatty breasts for pubertal breasts
  • Obesity likely lowers the threshold for onset in a subset of girls

• Onset of thelarche at 7 in NHB and MA girls likely normal but not in NHW girls.

• Pubic hair before 8 in any girl is not normal
## TABLE 1

**Early Pubertal Milestone Attainment in Girls With Normal and Excessive BMI**

<table>
<thead>
<tr>
<th>Landmark</th>
<th>Group</th>
<th>Estimated Attainment at Age 8.0 y, % (95% CI)*</th>
<th>Estimated Age (95% CI) at Attainment Percentile, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5th Percentile</td>
</tr>
<tr>
<td>Breast stage 2</td>
<td>10th–84th</td>
<td>All (N = 1299)</td>
<td>3.2 (0.3–6.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NHW (N = 374)</td>
<td>1.3 (0.0–3.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NHB (N = 431)</td>
<td>12.1 (4.7–19.4)b</td>
</tr>
<tr>
<td></td>
<td>≥85th</td>
<td>MA (N = 425)</td>
<td>19.2 (0.0–38.4)</td>
</tr>
<tr>
<td>Public hair stage 3</td>
<td>10th–84th</td>
<td>All (N = 615)</td>
<td>12.3 (2.3–22.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NHW (N = 369)</td>
<td>0.01 (0.0–0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NHB (N = 428)</td>
<td>3.0 (0.6–5.3)b</td>
</tr>
<tr>
<td></td>
<td>≥85th</td>
<td>MA (N = 418)</td>
<td>1.3 (0.0–3.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All (N = 605)</td>
<td>2.1 (0.0–5.2)</td>
</tr>
</tbody>
</table>

*Estimates that extrapolate below the age range of the data are reported as <8.0.

*Negative lower confidence limits were truncated to 0.
bP < .05 versus NHW subjects.
cP < .05 versus MA subjects.
### Table 3: Stage 3 Pubic Hair Attainment in Boys With Normal and Excessive BMI

<table>
<thead>
<tr>
<th>BMI Percentile</th>
<th>Group</th>
<th>Estimated Attainment at Age 10.0 y, % (95% CI)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Estimated Age (95% CI) at Attainment Percentile, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>10th–84th</td>
<td>All (N = 1313)</td>
<td>1.1 (0.0–2.6)</td>
<td>10.73 (10.20–11.13)</td>
</tr>
<tr>
<td></td>
<td>NHW (N = 330)</td>
<td>0.9 (0.0–2.4)</td>
<td>10.81 (10.09–11.28)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>NHB (N = 497)</td>
<td>1.6 (0.0–3.9)</td>
<td>10.26 (9.70–10.69)&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>MA (N = 308)</td>
<td>0.2 (0.0–0.5)</td>
<td>11.66 (11.08–12.02)</td>
</tr>
<tr>
<td>≥85th</td>
<td>All (N = 556)</td>
<td>2.4 (0.0–4.9)</td>
<td>10.45 (9.83–10.92)</td>
</tr>
</tbody>
</table>

**Notes:**

- <sup>a</sup> Estimated attainment at age 9.0 years was <0.01% for boys with normal BMI, overall and in each subgroup, and was 0.03% in boys with excessive BMI.
- <sup>b</sup> Negative lower confidence limits were truncated to 0.
- <sup>c</sup> <i>P</i> < .05 versus MA subjects.
- <sup>d</sup> <i>P</i> < .05 versus NHW subjects.
# NORMS

## TABLE 2  Menarche Attainment in Girls With Normal and Excessive BMI

<table>
<thead>
<tr>
<th>BMI Percentile</th>
<th>Group</th>
<th>Estimated Attainment at Age 9.0 y, % (95% CI)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Estimated Age (95% CI) at Attainment Percentile, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5th Percentile</td>
</tr>
<tr>
<td>10th–84th</td>
<td>All (N = 1394)</td>
<td>0.01 (0.0–0.03)</td>
<td>11.01 (10.66–11.27)</td>
</tr>
<tr>
<td></td>
<td>NHW (N = 410)</td>
<td>&lt;0.001 (0.0–0.004)</td>
<td>11.31 (10.92–11.62)</td>
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<tr>
<td></td>
<td>NHB (N = 453)</td>
<td>0.01 (0.0–0.04)</td>
<td>10.52 (9.94–10.85)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>MA (N = 455)</td>
<td>0.003 (0.0–0.01)</td>
<td>10.74 (10.38–11.04)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥85th</td>
<td>All (N = 671)</td>
<td>0.4 (0.0–1.2)</td>
<td>10.18 (9.47–10.65)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> For girls with normal BMI, attainment at age 8.0 years was too low to obtain confidence limits; for girls with excessive BMI, estimated attainment at age 8.0 years was 0.02%.

<sup>b</sup> Negative lower confidence limits were truncated to 0.

<sup>c</sup> P < .05 versus NHW subjects.

<sup>d</sup> P < .05 versus BMI 10th to 84th percentile.
MENARCHE

• No systematic, heterogeneous studies on the timing of menarche before the later half of the 20th century.
  • Small population studies, based on recall of grown women

• Most sources agree that the average age has declined
  • From 6th to 15th centuries in Europe, most women reached menarche on average at about 14 years old
  • Decline in age of menarche 17 to 13 in Europe from 1850 to 1960
  • 2011 Journal of obesity: Link earlier menarche with increased BMI
  • 2010 Pediatrics: Maternal risk factors associated with earlier attainment of menarche in female offspring included: smoking, maternal menarche < 12 years, early infant weight gain,
WHY MIGHT PUBERTY BE OCCURRING EARLIER?

• Obesity
• Endocrine disrupting compounds

• The problem is that these two proposed culprits cannot be untangled
  • Food with EDCs – obese people are eating more EDCs
  • EDC’s may be more prevalent in urban, low SES settings where there is a higher prevalence of obesity
WHY MIGHT PUBERTY BE OCCURRING EARLIER

Glutamate, NKB, Kisspeptins, Leptin

GABA

Development of:
- Penis
- Pubic hair
- Testes

Development of:
- Breasts
- Ovaries
- Uterus

Development of:
- Pubic hair
- Arm pit hair
- Acne
Figure 1
Schematic of the HPG axis and the

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-12-0449
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Printed in Great Britain
ACTIVATION OF HPG AXIS FROM FETUS TO CHILDHOOD TO PUBERTY AND ADULT LIFE

Figure 1 | Schematic of the activation of the hypothalamic–pituitary–testicular axis during fetal and postnatal life in humans. During fetal, early neonatal and pubertal development, a | pulsatile hypothalamic secretion of GnRH stimulates b | pituitary gonadotropin biosynthesis and secretion that, in turn, stimulates c | testicular steroid and peptide hormone production. The dotted line represents spermatogenesis, which occurs only after puberty. Abbreviations: AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; IB, inhibin B; LH, luteinizing hormone; T, testosterone. 

Bourvattier, 2012
SERUM LH PULSATILITY BY TIME OF DAY

Courtesy Medscape
‘PUBERTY IS METABOLICALLY GATED’

• Reproduction is a state of high energy requirement
• Biologically this is to prevent fertility in starvation states, when energy is insufficient
Figure 1
Schematic of the HPG axis and the
Within Hypothalamic Nuclei
Leptin and Kisspeptin

As well as glutamate, neurokinin B, etc.

Fig. 1. Tentative diagram for the potential mode of action of leptin on Kis1 and/or GnRH neurons. Direct (A), indirect (B) and independent (C) actions of leptin on Kis1 pathways, as putative mechanism for transmission of the regulatory effects of the adipose hormone on GnRH neurons, are depicted. Note, however, that primary actions of leptin in hypothalamic nuclei, such as the ventral premammillary nucleus (PMV), initially considered as kisspeptin-independent, do not necessarily exclude the possibility of some interplay with Kis1 circuits, which is represented as a dotted line projection. For further details, see Interplay of leptin and kisspeptins in the metabolic control of puberty. direct or indirect? and Other sites of action of leptin in the metabolic control of puberty sections. WAT: White adipose tissue; CNS: Central Nervous System.

Sanchez, 2013
KISSPEPTINS

• Products of the *Kiss1* gene
• Ligand for Gpr54 (Kiss1R) receptor
• Originally discovered in some patients with hypogonadotrophic hypogonadism
• Axons are ubiquitous in the hypothalamic nuclei
• Intimate connection between neurons expressing Kiss-1 and GnRH

Sanchez, 2013
KISSPEPTINS

• They are necessary upstream regulators of GnRH neurons, allowing for the pulsatile GnrH release

• Integrators of environmental and nutritional signals

• Thought to be involved in reproductive maturation, but also, brain sex differentiation as well as sex steroid feedback and regulation of ovulation.

Sanchez, 2013
Fig. 1. Tentative diagram for the potential mode of action of leptin on Kiss1 and/or GnRH neurons. Direct (A), indirect (B) and independent (C) actions of leptin on Kiss1 pathways, as putative mechanisms for transmission of the regulatory effects of the adipose hormone on GnRH neurons, are depicted. Note, however, that primary actions of leptin in hypothalamic nuclei, such as the ventral premammillary nucleus (PMV), initially considered as kisspeptin-independent, do not necessarily exclude the possibility of some interplay with Kiss1 circuits, which is represented as a dotted line projection. For further details, see Interplay of leptin and kisspeptins in the metabolic control of puberty: direct or indirect? and Other sites of action of leptin in the metabolic control of puberty sections. WAT: White adipose tissue; CNS: Central Nervous System.
LEPTIN

- Hormone produced in adipocytes, discovered 1994
- Was originally thought to be the ‘obesity gene’
- In fact only a small majority of obese patients have true leptin or leptin R abnormality.
- However, it is a **barometer** of energy sufficiency
- Levels in circulation are proportional to fat mass
LEPTIN

• Involved in hypothalamic circuits that are crucial to hunger and satiety
• Leptin deficient mice (ob/ob) – fat and infertile
LEPTIN’S ROLE IN PUBERTY

• Direct vs. indirect effect on Kiss1 system
• Peripheral stimulation of the gonad and interaction with insulin
• Direct effects on bone to achieve substantial somatic growth which may be one of the requisites of puberty
BEYOND LEPTIN: WHY OBESITY MAY AFFECT PUBERTAL TIMING

• Adiposity is the metabolic gatekeeper (or one of them) to pubertal initiation
  • Direct and indirect effects of leptin
• Peripubertal obesity reduces SHBG, making sex steroids more bioavailable
• Aromatazation of circulating adrenal androgens to estrogens can perhaps jump start puberty?
• Hyperinsulinism promote gonadal and adrenal sex steroid synthesis.
Pediatric Reports, 2012
SHIFT TO EARLIER PUBERTY

• Just continued ‘improvement’ in nutrition and OVER nutrition as seen in the secular trend

• Are there environmental compounds that are hormonally active that are responsible for lower sperm counts, hypospadias and cryptorchidism and the possible lower age of pubertal changes
ENDOCRINE DISRUPTING COMPOUNDS
WHAT ARE EDC’S
WHAT ARE EDC’S
ENDOCRINE DISRUPTING COMPOUNDS

• Synthetic or natural compounds that perturbs endogenous endocrine action
• Mechanisms are multiple:
  • Estrogen receptor binding and activation
  • Post signaling modifications
  • Modulation of how hormones/receptors/cofactors are made, their activity and their degradation
  • Inhibition of androgen production
  • Developmental programming/embryogenesis
### Chemicals and Their Effects

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Structure</th>
<th>Mechanism</th>
<th>Reproductive toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES (synthetic estrogen)</td>
<td><img src="image" alt="DES Structure" /></td>
<td>ER agonist</td>
<td>Geritourinary development&lt;br&gt;Reproductive tract tumors</td>
</tr>
<tr>
<td>Methoxychlor (insecticide)</td>
<td><img src="image" alt="Methoxychlor Structure" /></td>
<td>Metabolite is ER agonist</td>
<td>Geritourinary development&lt;br&gt;Puberty&lt;br&gt;Spermatogenesis</td>
</tr>
<tr>
<td>DDT (insecticide)</td>
<td><img src="image" alt="DDT Structure" /></td>
<td>ER agonist&lt;br&gt;DDE (metabolite) is AR antagonist</td>
<td>Tesicular descent&lt;br&gt;Puberty&lt;br&gt;Spermatogenesis</td>
</tr>
<tr>
<td>Bisphenol A (epoxy resin/poly carbonate)</td>
<td><img src="image" alt="Bisphenol A Structure" /></td>
<td>Anti-androgen ER agonist</td>
<td>Sex differentiation&lt;br&gt;Prostate development&lt;br&gt;Puberty&lt;br&gt;Reproductive tract tumors</td>
</tr>
<tr>
<td>PCB (insulator/coolant)</td>
<td><img src="image" alt="PCB Structure" /></td>
<td>ER agonist&lt;br&gt;AR antagonist&lt;br&gt;Inhibits sex steroid synthesis</td>
<td>Sex differentiation&lt;br&gt;Neuroendocrine axis&lt;br&gt;Puberty&lt;br&gt;Spermatogenesis</td>
</tr>
<tr>
<td>Phthalate (plasticizer)</td>
<td><img src="image" alt="Phthalate Structure" /></td>
<td>Anti-androgen&lt;br&gt;ER agonist&lt;br&gt;Inhibits androgen synthesis</td>
<td>Sex differentiation&lt;br&gt;Geritourinary development&lt;br&gt;Spermatogenesis</td>
</tr>
<tr>
<td>Genistein (plant estrogen)</td>
<td><img src="image" alt="Genistein Structure" /></td>
<td>ER antagonist&lt;br&gt;ER agonist</td>
<td>Neuroendocrine axis&lt;br&gt;Puberty</td>
</tr>
<tr>
<td>Dioxin (organochlorine)</td>
<td><img src="image" alt="Dioxin Structure" /></td>
<td>Anti-estrogen&lt;br&gt;Anti-androgen&lt;br&gt;Inhibits androgen synthesis</td>
<td>Geritourinary development&lt;br&gt;Neuroendocrine axis&lt;br&gt;Puberty&lt;br&gt;Spermatogenesis</td>
</tr>
</tbody>
</table>

**Note:**
- ER: Estrogen Receptor
- AR: Androgen Receptor
- DES: diethylstibestrol
- DDE: dichlorodiphenyltrichloroethane
- PCB: polychlorinated biphenyl
- Phytoestrogens: natural plant compounds that mimic estrogen effects.

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Source: Zawatski and Lee, 2013

http://joe.endocrinology-journal.org

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Printed in Great Britain

Published by Bioscientifica Ltd.
EDC’S AND PUBERTY – ANIMAL STUDIES

- Central and peripheral effects
- Prenatal effects
  - HPG axis development – ready to work by 12 week gest
- Pre/Postnatal effects
  - Sex steroid levels at crucial times are important for Kiss1r mRNA expression
- Some compounds are sexually dimorphic effects
- Some have divergent effects depending on the time of exposure.
Relevance
WHY IS THIS IMPORTANT?

- **Practical standpoint** – should we be referring everyone who has breast development at 7y6m?
  - My best answer is
    - If it’s a boy
  - My safe answer is
    - We don’t know.
  - But a starting point is to see if there are reasons to believe that this is not a normal process. Mom with menarche at 14 y, not AA ethnicity, thin
WHY IS THIS IMPORTANT?

• Is this just the new normal?
  • Is this just a marker of better nutrition? Of overnutrition?
  • Will genes eventually catch up to the environment?
• Isn’t it the same as revamping the BMI curve to make the overweight kids the new normal?
WHY IS THIS IMPORTANT?

• Are there consequences to public health?
  • Psychological
    • Poor self image, risk for substance abuse, risky behaviors, depression, eating disorders
  • Reproductive cancers in women with earlier menarche
  • Premature adrenarche associated with obesity, metabolic syndrome, PCOS, frank cardiovascular disease
PUBERTY IS A SENSOR

Of the proper interplay between genes and the environment.

Sanchez, 2013


http://www.who.int/maternal_child_adolescent/topics/adolescence/dev/en/

http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm
