Statural Growth Impairment in Pediatric Crohn's Disease

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Weill Cornell Medical College

Learning Objectives

- Review what is known about the etiology of statural growth impairment and sex differences in statural growth impairment in pediatric Crohn's disease
- Illustrate the importance of utilizing bone age in interpreting statural growth in pediatric Crohn's disease
- Strategize next steps to improve our understanding of the underlying mechanisms of statural growth impairment in pediatric Crohn's disease in order to optimize management

Outline

- Background
- Multicenter Growth Study
- Future Directions

Background:

Growth Impairment

Commonly Used Definitions of Growth Impairment

- Height below the 3rd-5th percentile
- Decrease in height velocity below the 3rd-5th percentile
- Fall off the child's growth curve

Prevalence

Negative height Z score	72%
Height Z score < -1.64	23%
Decreased height velocity prior to diagnosis	88%
Reduction in height velocity before intestinal symptoms	42%
Height velocity < 4 cm/year	24%

Kanof et al, Gastroenterology, 1988
Motil et al, Gastroenterology, 1993

Growth abnormalities persist in newly diagnosed children

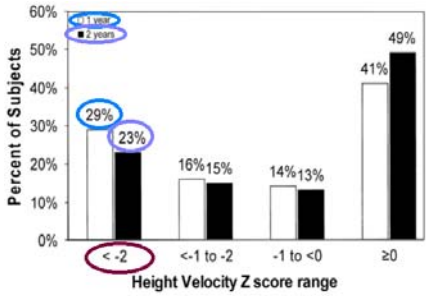


FIG. 3. Height velocity *z* scores at 1 year and 2 years.

Pfefferkorn et al, J Pediatr Gastroenterol Nutr, 2009

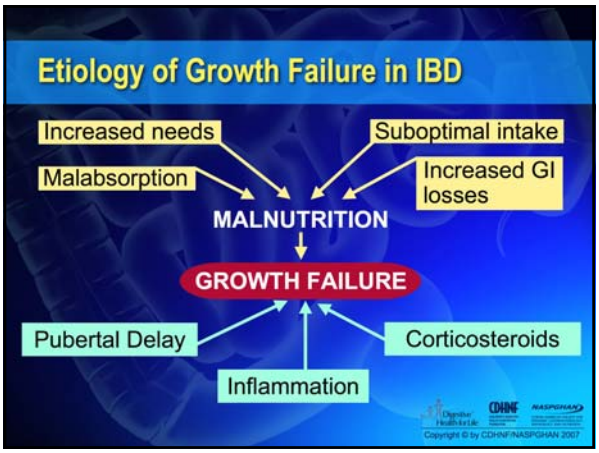
NIH/NIDDK's Opportunities & Challenges in Digestive Diseases Research: Research Objectives

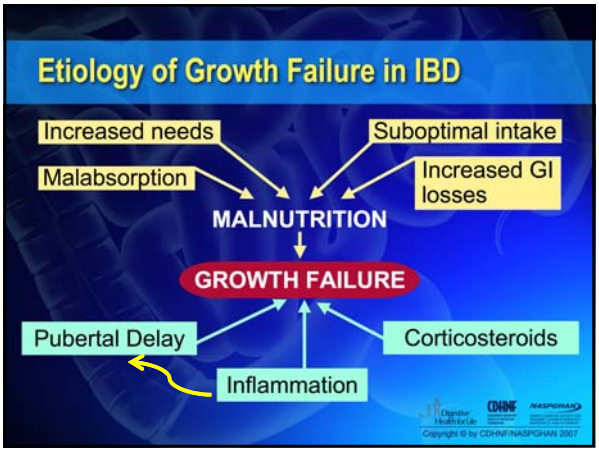
- Ameliorate or prevent adverse effects of IBD on growth and development in children and adolescents
- Define the mechanisms that produce growth delay in pediatric IBD patients
- Identify approaches that enable normal growth and development within the context of pediatric IBD

National Commission on Digestive Diseases, 2009

Etiologies of Statural Growth Impairment in Pediatric Crohn's Disease

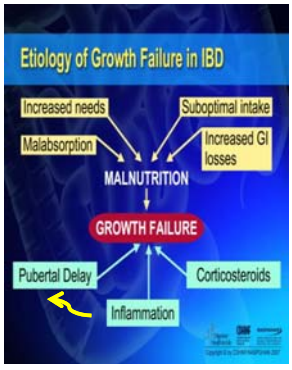
What We Know





Some reports point to disease severity as the major determinant of growth.

Motil et al, Gastroenterology, 1993
Griffiths et al, Gut, 1993
Wine et al, Pediatrics, 2004



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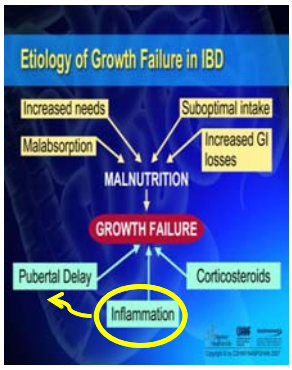
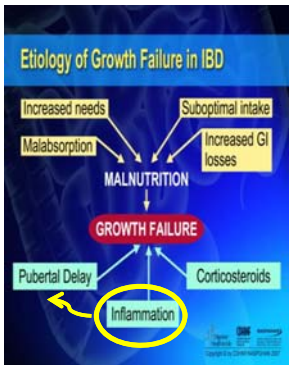


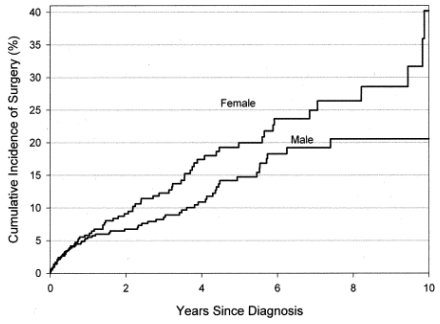
Taken together, the available data suggest that the negative impact of inflammation on growth is greater in males.



Sex Differences in Statural Growth Impairment in Crohn's Disease

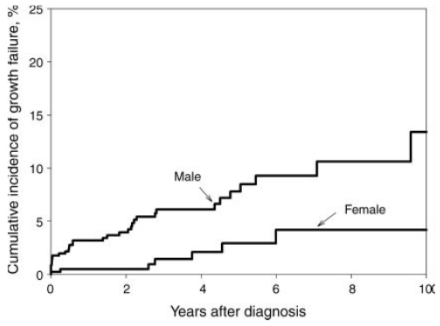
What We Know

Cumulative Incidence of Surgery



Gupta et al, Pediatric IBD Consortium, Gastroenterology, 2006

Cumulative Incidence of Growth Impairment



Gupta et al, Pediatric IBD Consortium, Pediatrics, 2007

Growth of Children with Crohn's disease

Sex	Initial Height Z Score	Ultimate Height Z Score	Changes in Height Z Scores
Female (N=25)	-1.01 (1.06)	-0.48 (0.91)	0.66 (1.27)
Male (N=42)	-1.22 (1.30)	-1.02 (1.19)	0.16 (0.90)
P=0.02			

Griffiths et al, Gut, 1993

Growth, Body Composition, & Nutritional Status in Children & Adolescents With Crohn's Disease

Deficits in Growth & Nutritional Status in Males with Crohn's versus Male Controls

Females: No Difference

Male subjects

	Control (n = 29)	CD (n = 84)	P
WAZ	0.26 ± 0.95	−0.66 ± 1.18	0.00002
HAZ	0.28 ± 0.93	−0.81 ± 1.14	0.00001
AHAZ	0.4 ± 1.03	−1.05 ± 1.03	0.00001
ACZ	−0.01 ± 1.02	−0.58 ± 1.10	0.013
TSFZ	−0.05 ± 0.64	0.06 ± 0.77	0.47
UAMAZ	0.36 ± 1.30	−0.53 ± 1.27	0.0015
EZ	0.36 ± 0.97	−0.67 ± 1.04	0.007
CFR	0.44 ± 0.02	0.42 ± 0.01	0.15

Female subjects

Control (n = 37)	CD (n = 48)	P
−0.08 ± 0.98	−0.14 ± 1.19	0.80
−0.16 ± 0.98	−0.46 ± 1.38	0.27
−0.22 ± 0.92	−0.62 ± 1.37	0.15
−0.008 ± 0.99	−0.11 ± 0.88	0.88
−0.34 ± 0.86	−0.11 ± 0.81	0.21
0.45 ± 1.17	0.27 ± 1.07	0.32
−0.33 ± 1.06	−0.28 ± 1.32	0.83
0.42 ± 0.01	0.39 ± 0.01	0.23

Sentongo et al, J Pediatr Gastroenterol Nutrition, 2000

Nutritional Status & Growth in Pediatric Crohn's Disease: A Population-Based Study

Sex Differences in Ht Z Score at Maximal Follow-Up

Sex	Height Z Score	P Value
Males (N=156)	-0.43	0.0002
Females (N=105)	-0.04	

Vasseur et al, Am J Gastroenterol, 2010

Final Adult Height Childhood- vs Adult- Onset Crohn's Disease

Sex	Childhood-Onset CD (N = 206)	Adult-Onset CD (N = 412)	P-Value
Males	172.8 ± 7.4	176.4 ± 6.5	<0.001
Females	162.2 ± 5.9	163.1 ± 6.0	NS
Total	167.9 ± 8.6	170.3 ± 9.1	<0.001

Pigneur et al, Inflamm Bowel Dis, 2010

NIH to balance sex in cell and animal studies

Janine A. Clayton and **Francis S. Collins** unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males

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NIH Takes Steps to Address Sex Differences in Preclinical Research

May 14, 2014

Over the past two decades, **we have learned a great deal about how men and women respond differently to medications**. This knowledge came after a concerted effort in the early '90s to increase the number of women in NIH-funded clinical research. **Today, just over half of NIH-funded clinical research participants are women**. Unfortunately, experimental design in cell and animal research has not always followed suit. **An over-reliance on male animals, and neglect of attention to the sex of cells, can lead to neglect of key sex differences that should be guiding clinical studies, and ultimately, clinical practice**. NIH is taking action to address this shortfall as outlined by Janine A. Clayton, M.D., Director of the NIH Office of Research on Women's Health, and me in the *Nature* Comment below.

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

NIH OFFICE OF RESEARCH ON WOMEN'S HEALTH (ORWH)

Director's Page

Considering Sex as a Biological Variable: in the NIH Guide

June 9, 2015

This week's NIH Guide contains a notice announcing our expectation that beginning in fall 2016, scientists will account for the possible role of sex as a biological variable (SABV) in vertebrate animal and human studies. Pending approval from the Office of Management and Budget, the NIH Office of Extramural Research will be updating instructions for applicants as part of NIH's expectations to enhance reproducibility through rigor and transparency. In short, applicants will be asked to include SABV information in the Research Strategy section of applications, and study sections will be reviewing this information.


Director's Page

SundayReview | EDITORIAL

Why Science Needs Female Mice

New York Times
July 18, 2015

Scientific research has a gender gap, and not just among humans. In many disciplines, the animals used to study diseases and drugs are overwhelmingly male, which may significantly reduce the reliability of research and lead to drugs that won't work in half the population.

A new study published in the journal Nature Neuroscience suggests that research done on male animals may not hold up for women. Its authors reported that hypersensitivity to pain works differently in male and female mice. For males, immune cells called microglia appear to be required for pain hypersensitivity, and inhibiting their function also relieves the pain. But in female mice, different cells are involved, and targeting the microglia has no effect. If these differences occur in mice, they may occur in humans too. This means a pain drug targeting microglia might appear to work in male mice, but wouldn't work on women.

Failure to consider gender in research is very much the norm. According to one analysis of scientific studies that were published in 2009, male animals outnumbered females 5.5 to 1 in neuroscience, 5 to 1 in pharmacology, and 3.7 to 1 in physiology. Only 45 percent of animal studies involving depression or anxiety and only 38 percent involving strokes used females, even though these conditions are more common in women.

In 1994, the National Institutes of Health confronted gender imbalance in clinical drug trials and began requiring that women and minorities be included in clinical studies; women now make up around half of clinical trial participants. In June, the N.I.H. announced that it would begin requiring researchers to take gender into account in preclinical research on animals as well.

Under the new requirements, researchers applying for N.I.H. grants in January 2016 and later will need to show "strong justification" if they plan to study only one sex. Justifications can include study of sex-specific conditions like ovarian cancer or limited availability of subjects of both sexes (as with primates).

This new policy for grants sends a good message to scientists and drug makers on the importance of considering sex in designing research projects, if they want to understand diseases that appear to affect men and women differently and develop medicines effective for those diseases.

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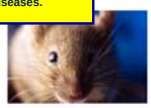

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THE WALL STREET JOURNAL.

Men and Women Differ in How They Experience Disease, Respond to Treatment

Alzheimer's, nicotine addiction and lung cancer are among the areas where big differences have been found

By AMY WESTERVELT

The Wall Street Journal
Sept 26, 2015

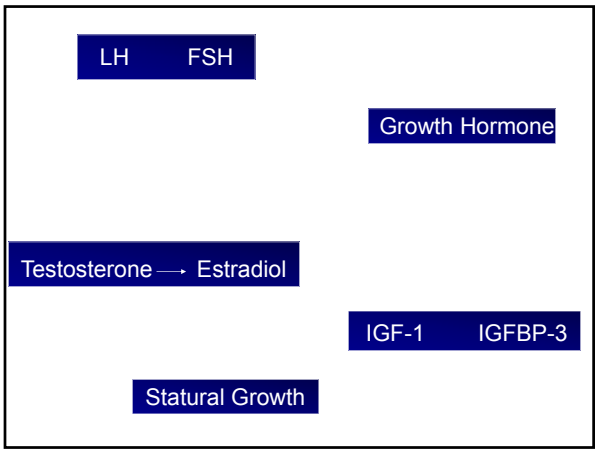
Male-Female Dichotomy in Risk for Developing Statural Growth Impairment

Male-Female Dichotomy in Risk for Developing Statural Growth Impairment

Window for furthering our understanding of the effects of inflammation on growth in ***both sexes***

Major Endocrinologic Regulators of Statural Growth

- Growth Hormone/Insulin-Like Growth Factor-1 Axis
- Hypothalamic-Pituitary-Gonadal Axis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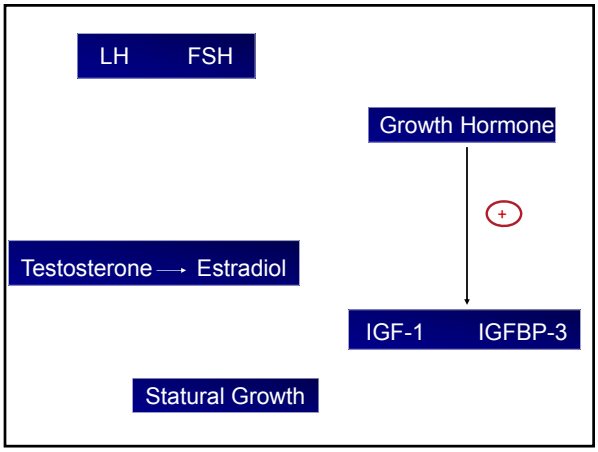
Testosterone ⟶ Estradiol
IGF-1 IGFBP-3
Statural Growth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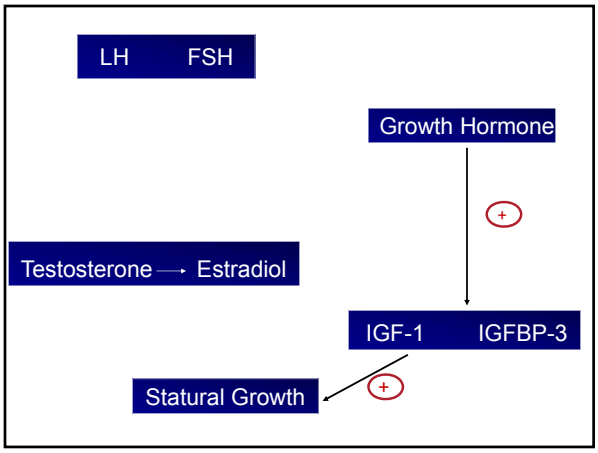
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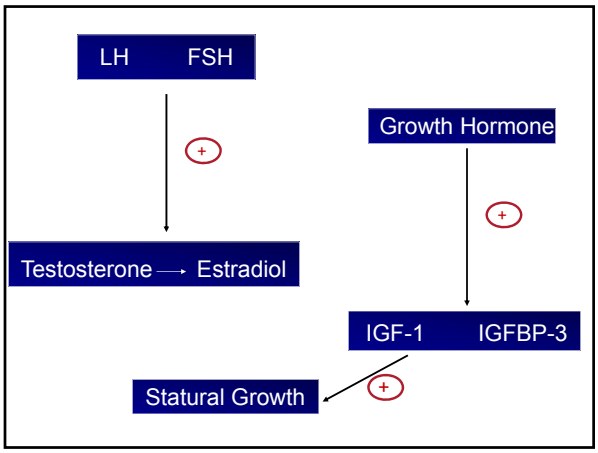
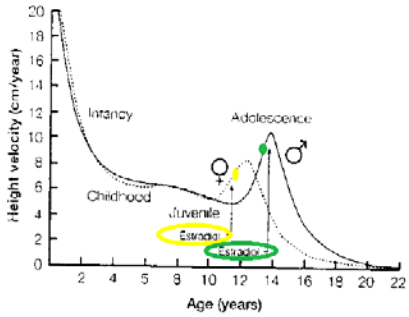


Estrogen, Bone, Growth, & Sex: A Sea Change in Conventional Wisdom

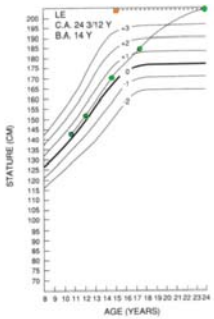


Grumbach et al, J Pediatr Endocrinol Metab, 2000

Aromatase Deficiency in Male & Female Siblings Caused by a Novel Mutation & the Physiological Role of Estrogens

Bone Age = 14 Years

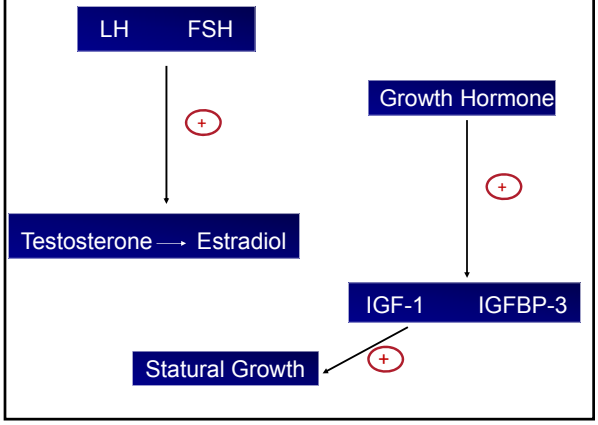
Chronological Age = 24 Years

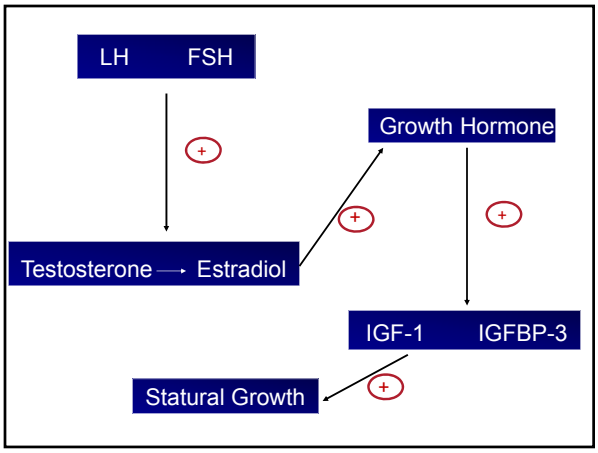


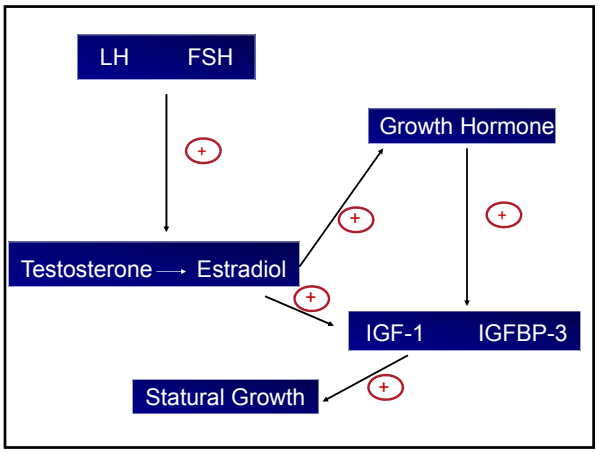
Morishima et al, J Clin Endocrinol Metab, 1995

Estrogen: Consequences & Implications of Human Mutations in Synthesis & Action

Grumbach & Auchus, J Clin Endocrinol Metab, 1999



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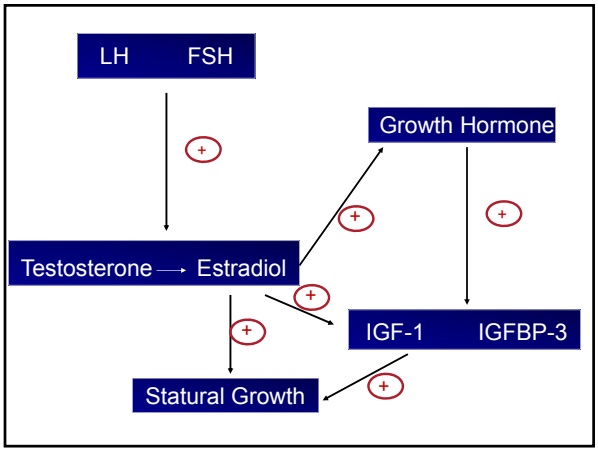
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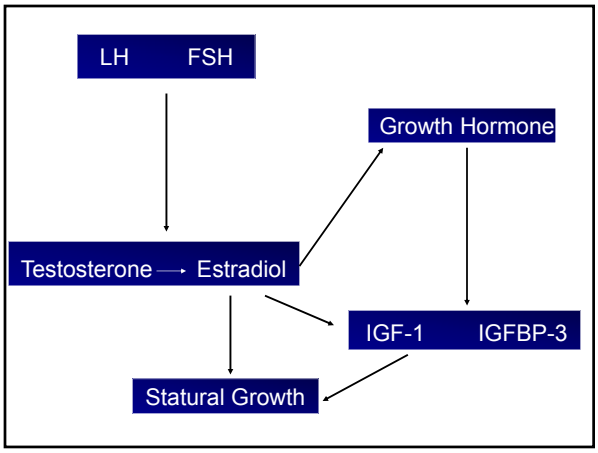
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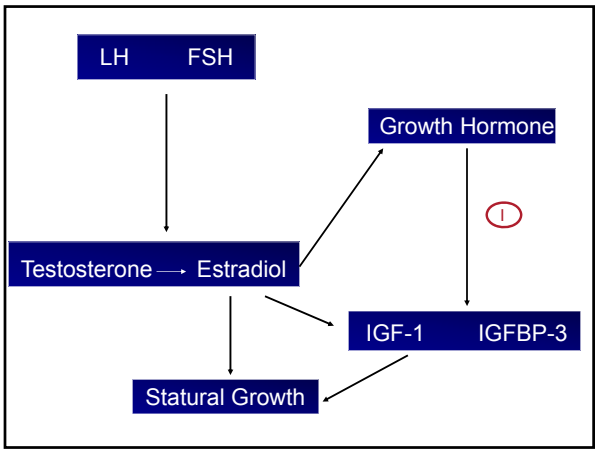
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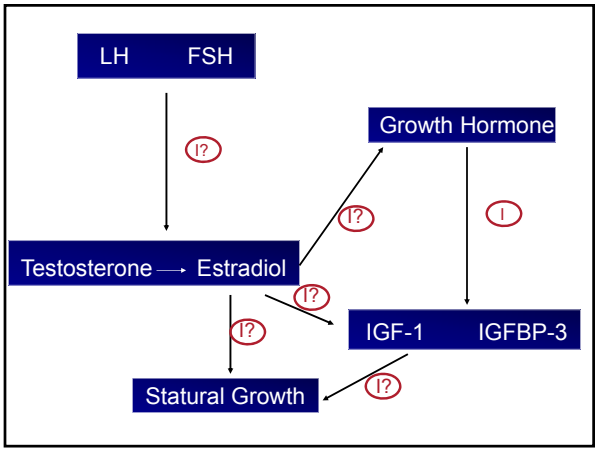
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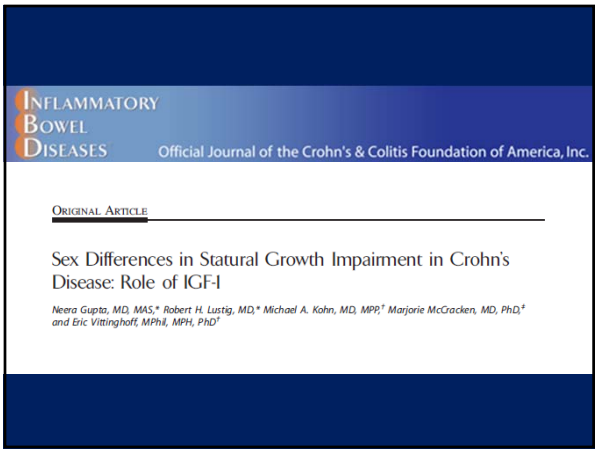

INFLAMMATORY
BOWEL
DISEASES
Official Journal of the Crohn's & Colitis Foundation of America, Inc.
ORIGINAL ARTICLE
Sex Differences in Statural Growth Impairment in Crohn's Disease: Role of IGF-I
Neera Gupta, MD, MAS,* Robert H. Lustig, MD,* Michael A. Kohn, MD, MPP,† Marjorie McCracken, MD, PhD,‡ and Eric Vittinghoff, MPhil, MPH, PhD†

Hypotheses

- Primary:
  - IGF-1 levels are lower in males compared with females with Crohn's disease
- Secondary:
  - Inflammatory markers predict IGF-1 levels in patients with Crohn's disease

IGF-1 Z Scores Are Lower in Males

Z Score	IGF-1 Z Scores				
	Female	Male	Sex Difference*	95% CI	P
CA-Z (N=82)	-0.97± 1.08 (-2.87, 0.97)	-1.46 ± 1.10 (-3.61, 0.94)	-0.50	-0.99, -0.02	.04
BA-Z (N=49)	-0.12 ± 1.49 (-2.73, 2.74)	-1.26 ± 1.16 (-3.23, 0.94)	-1.24	-2.03, -0.45	.003

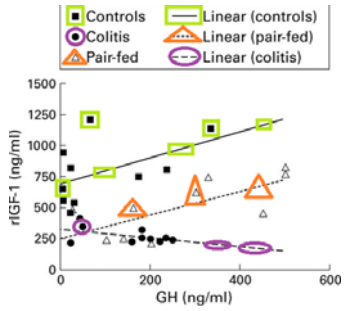
IGFBP-3 Z Scores Are Lower in Males

Z Score	IGFBP-3 Z Scores				
	Female	Male	Sex Difference*	95% CI	P Val
CA-Z (N=82)	-0.25 ± 1.11 (-1.79, 2.50)	-0.95 ± 1.06 (-3.08, 1.73)	-0.71	-1.19, -0.23	.004
BA-Z (N=49)	0.27 ± 1.34 (-1.18, 3.44)	-0.98 ± 0.73 (-2.37, 1.03)	-1.26	-1.87, -0.65	<.001

Inflammation Predicts IGF Z Scores

Marker	ESR		CRP		Albumin		BMI Z	
Outcome	ΔR^2	P Val	ΔR^2	P Val	ΔR^2	P Val	ΔR^2	P Val
IGF-1 CA- Z	10.0	.002	17.1	.0001	6.7	.01	10.7	.007
IGF-1 BA-Z	9.1	.02	13.7	.003	19.5	.001	3.2	.16
IGFBP-3 CA- Z	5.5	.07	3.5	.07	0.2	.65	0.2	.67
IGFBP-3 BA-Z	5.6	.14	3.6	.11	0.0	.95	0.2	.70

Growth failure occurs through a decrease in insulin-like growth factor 1 which is independent of undernutrition in a rat model of colitis



Ballinger et al, Gut, 2000

Inflammatory Markers Correlate with Hormone Levels in Males

	Female				Male			
	Estradiol Z (CA)	Estradiol Z (BA)	FSH Z (CA)	FSH Z (BA)	Testosterone Z (CA)	Testosterone Z (BA)	LH Z (CA)	LH Z (BA)
ESR	-0.06* (.73)**	-.13 (.63)	-0.11 (.52)	-0.28 (.28)	-0.35 (.02)	-0.49 (.004)	-0.27 (.06)	-0.53 (.002)
CRP	-0.12 (.50)	0.07 (.80)	-0.08 (.64)	-0.06 (.82)	-0.31 (.03)	-0.38 (.03)	-0.12 (.43)	-0.52 (.003)
Alb	0.18 (.29)	0.23 (.38)	0.20 (.25)	0.20 (.43)	0.40 (.005)	0.48 (.005)	0.26 (.07)	0.51 (.003)

*
**

Delayed Puberty and Response to Testosterone in a Rat Model of Colitis

- Colitic versus normal rats
  - Testosterone reduced in colitic males
  - No difference in estradiol levels in colitic vs normal females

Azooz et al, Am J Physiol Regul Integr Comp Physiol, 2001

Results

- Mean BA-Z score= -1.4 ± 1.5 (std dev)
- BA-Z score < -2 in 41%
- Lower BA-Z scores in females (p=.02)

Chronologic Age vs Bone Age for Interpretation of Growth

TABLE 3. Comparison between Chronological Age and Bone Age for Interpretation of Growth

Growth Parameter	Z Score Difference*	95% CI	*P*-value
Height	0.73	0.45 to 1.01	<0.0001
Weight	0.51	0.29 to 0.74	<0.0001
BMI	0.23	0.13 to 0.33	<0.0001

*Z score difference = growth parameter BA-Z score minus growth parameter CA-Z score.

Chronologic Age vs Bone Age for Interpretation of Growth

TABLE 3. Comparison between Chronological Age and Bone Age for Interpretation of Growth

Growth Parameter	Z Score Difference*	95% CI	*P*-value
Height	0.73	0.45 to 1.01	<0.0001
Weight	0.51	0.29 to 0.74	<0.0001
BMI	0.23	0.13 to 0.33	<0.0001

*Z score difference = growth parameter BA-Z score minus growth parameter CA-Z score.

Percentile Difference (CA vs BA for Interpretation of Growth)

CA-Z Score	CA-Percentile	BA-Z score	BA-Percentile
-2	2.3%	-1.27	10.2%
-1	15.9%	-0.27	39.4%

Percentile Difference (CA vs BA for Interpretation of Growth)

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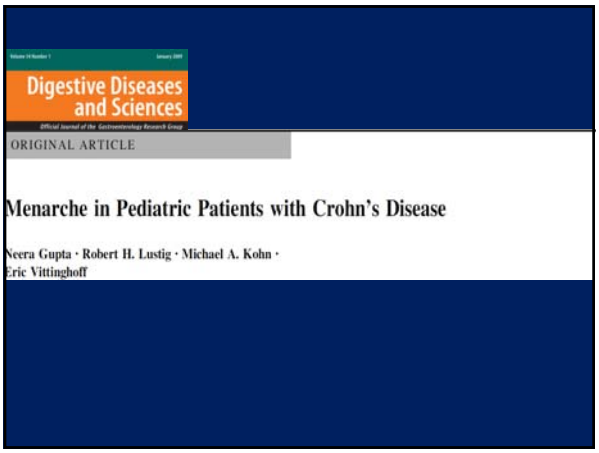
Take-Home Message

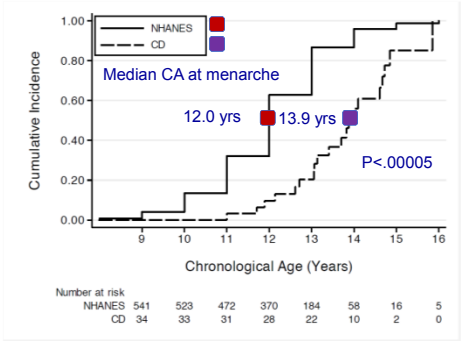
Bone age measurements allow clinically meaningful interpretation of statural growth
—a dynamic marker of disease status

NewYork-Presbyterian
Phyllis and David Komansky Center for Children's Health

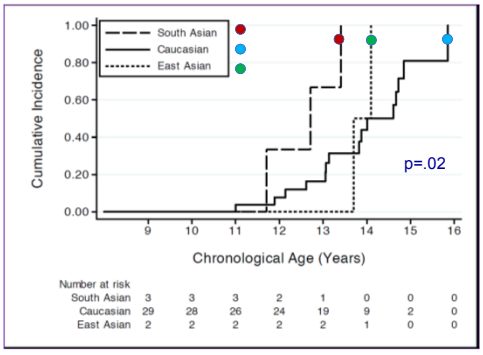
Weill Cornell Medical College



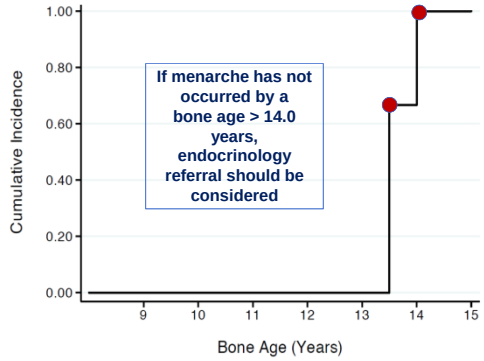
Age at Menarche



CA at Menarche by Race in CD



Bone Age at Menarche in CD



Additional Background

- Sex differences in inflammatory cytokine expression have been reported in hepatic ischemia, multiple sclerosis, and sepsis

Mizokami et al, J Urol 2000; Hong et al, Mol Cell Biol, 2004

- *In vitro* models suggest that inflammatory cytokines (TNF-α) reduce testosterone

Crockett et al, J Inflamm , 2006; Nguyen et al, J Neurol Sci 2003; Schroder et al, Arch Surg 1998

- Reduced androgen levels in males with CF, JIA, SLE

Boas et al, Pediatrics, 1996; Khalkhali-Ellis et al, Clin Exp Rheumatol 1998; Athreya et al, J Rheumatol 1993; Carrabba et al, Clin Rheumatol, 1985

Additional Background

- Growth impairment is a common complication of many chronic inflammatory diseases
- Crohn's disease - *model* for studying effects of inflammation on statural growth

Funded by NICHD R01 HD075929

NewYork-Presbyterian Phyllis and David Komansky Center for Children's Health

Weill Cornell Medical College

Purpose

- Improve our understanding of mechanisms of growth impairment
  - ➢Develop new targeted medical treatment strategies to improve height velocity and final adult height
  - ➢Optimize current treatment approaches in high risk patients
- Identify high risk patients

Growth Study Team


Neera Gupta
Principal Investigator


Howard Andrews
Director, DCC


Cheng-Shiun Leu
Biostatistician


Robert Lustig
Pediatric Endocrinologist


Joel Rosh
Site PI


Francisco Sylvester
Site PI

NewYork-Presbyterian Phyllis and David Komansky Center for Children's Health

Weill Cornell Medical College

Columbia University Medical Center

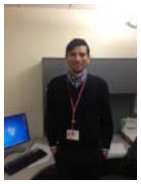
UCSF Benioff Children's Hospital

Goryeb Children's Hospital

UNC North Carolina Children's Hospital

WCMC Growth Study Team

To Be Hired
Research Study
Coordinator



Rafael Aguilar
Research Study Coordinator

Jeannie Hogg
Registered Dietician

Tejal Shah
DMS
Programmer

Drury Philip
Senior Research Technician
Biomarkers Core Lab

Francisco Santiago
Research Specialist
Biomarkers Core Lab

NewYork-Presbyterian
Phyllis and David Komansky
Center for Children's Health

Weill Cornell Medical College

Growth Study Goals

- Determine sex differences in the longitudinal impact of inflammation on
  - GH/IGF-1 axis
  - Hypothalamic-pituitary-gonadal axis
  - Height velocity
    - Most sensitive parameter for detecting impaired statural growth

Growth Study Goals

- Determine whether sex differences in the inflammatory cytokine profile exist
  - TNF-α
  - IL-1β
  - IL-6
  - IL-1RA
  - Explain the apparent sexual dimorphism in the impact of inflammation on growth?

Growth Study Goals

- Develop a predictive model for each sex
  - ➢Identify pts at high risk for growth impairment refractory to standard therapeutic approaches
    - Narrow therapeutic window to intervene to improve growth
    - Candidates for early intervention with more aggressive therapy?

Participants

- N = 125
- Inclusion criteria based on bone age
  - – Females: BA 9 – 12 years
  - – Males: BA 10 -14 years
    - Capture
      - – puberty based on the lower BA limit
      - – pubertal growth spurt based on the upper BA limit

Study Procedures

Timeline	-3 Months	Zero	6 Months	12 Months	18 Months	24 Months
Key Study Procedures	Routine Visit (Screening)	Study Visit 1	Study Visit 2	Study Visit 3	Study Visit 4	Study Visit 5
Bone Age	•			•		•
Medical History	•	•	•	•	•	•
Clinical & Self- Tanner Exam	•	•	•	•	•	•
Wt/Ht	•	•	•	•	•	•
Nutrient Intake Assessment		•		•		•
Blood Draw		•	•	•	•	•

Future Directions

- Ancillary studies of enrolled cohort
- Growth in Pediatric Ulcerative Colitis
- Multicenter RCT
  - Eligibility criteria:
    - "high risk" patients identified by prediction models for each sex
  - Examine early intervention with aggressive therapy

Growth Center for Children with Chronic Inflammatory Diseases (GCC-CID's)

- Multidisciplinary patient care and research center
  - Improve our understanding of the impact of inflammation on statural growth
  - Optimize treatment strategies

Take Home Messages

- Active inflammation may contribute to growth impairment in a patient who appears clinically well (no intestinal symptoms)
- Consider skeletal maturation and pubertal status in the interpretation of statural growth
- Statural growth should help guide therapeutic decisions
- Consider effects of sex on outcomes

Take Home Messages

- Inform patients of opportunities to participate in research studies
- Collaborate—team science is essential
- Evidence-based medicine should drive our clinical care

Research Funding

- NICHD R01 075929
- NIDDK K23 077734
- CDHNF (NASPGHAN Foundation)/CCFA Award for New Investigators
- CCFA Career Development Award

Thank You

Growth Study

Sex Differences in Statural Growth Impairment in Pediatric Crohn's Disease

@NeeraGuptaMD

#GrowthStudy

Extra Slides

Weill Cornell Medical College

Newyork-Presbyterian Phyllis and David Komansky Center for Children's Health

Growth Study

Sex Differences in Statural Growth Impairment in Pediatric Crohn's Disease

males-ages 9 to 15 years—and—females-ages 8 to 13 years Crohn's disease

We are learning about growth in pediatric patients with Crohn's disease with the hope that we may improve the care of pediatric patients with inflammatory bowel disease.

Mr. Rafael Aguilar, Research Coordinator, at 646-962-4968 or raa2030@med.cornell.edu or Dr. Neera Gupta at (646) 962-3869.

Growth Study

Growth Impairment Definitions for Our Study

- Height Velocity Z Score < -1.66
- Change in Height Velocity Z score of -0.5 from the screening visit
- Height Z Score < -1.66

Z Scores Based on Bone Age

Definition of "High Risk" for Our Study

- Patients who meet the definition of growth impairment despite standard treatment approaches
- Establish prediction model separately for each sex
  - well-known sex differences in growth impairment

NIH to balance sex in cell and animal studies

- Just over half of NIH-funded clinical-research participants are women
- Example of importance of studying both sexes in clinical research:
  - Medications have
    - different preventive effects in women and men
    - different optimal dosing in women and men
    - higher rates of adverse reactions in women

Clayton & Collins, Nature, May 2014

NIH to balance sex in cell and animal studies

- Over-reliance on male animals and cells in pre-clinical research
- Obscures key sex differences that could help guide clinical studies

Clayton & Collins, Nature, May 2014

NIH to balance sex in cell and animal studies

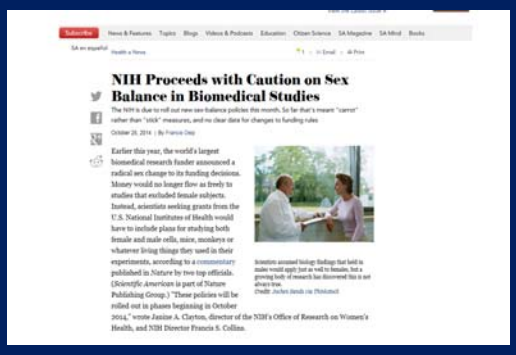
- Lack of understanding about the potential magnitude of the effect of sex on the outcome being measured
- Inadequate analysis of data by sex
  - Irreproducibility in preclinical biomedical research

Clayton & Collins, Nature, May 2014

NIH to balance sex in cell and animal studies

- NIH developing policies requiring reporting of plans to balance male and female cells and animals in preclinical studies
- Policies will be rolled out in phases beginning October 2014

Clayton & Collins, Nature, May 2014



NIH Proceeds with Caution on Sex Balance in Biomedical Studies

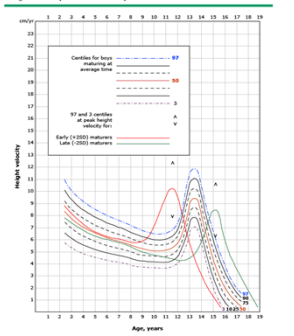
The NIH is due to roll out new sex-balance policies this month. So far that's meant "carrot" rather than "stick" measures, and no clear data for changes to funding rules

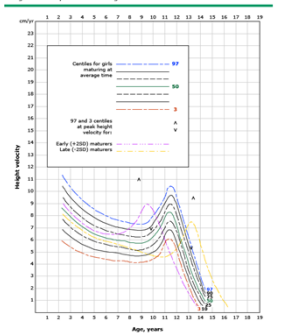
October 28, 2014 | By Francie Diep

Earlier this year, the world's largest biomedical research funder announced a radical sex change to its funding decisions. Money would no longer flow as freely to studies that excluded female subjects. Instead, scientists seeking grants from the U.S. National Institutes of Health would have to include plans for studying both female and male cells, mice, monkeys or whatever living things they used in their experiments, according to a commentary published in *Nature* by two top officials. (*Scientific American* is part of Nature Publishing Group.) "These policies will be rolled out in phases beginning in October 2014," wrote Janine A. Clayton, director of the NIH's Office of Research on Women's Health, and NIH Director Francis S. Collins.

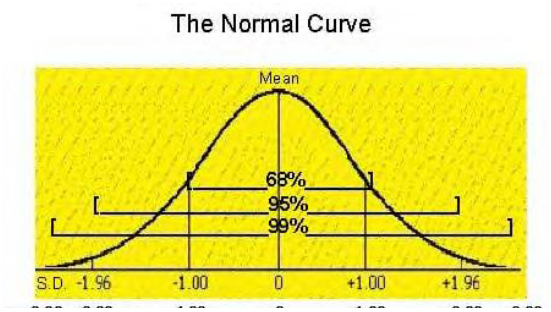
NIH Proceeds with Caution in Sex Balance on Biomedical Studies

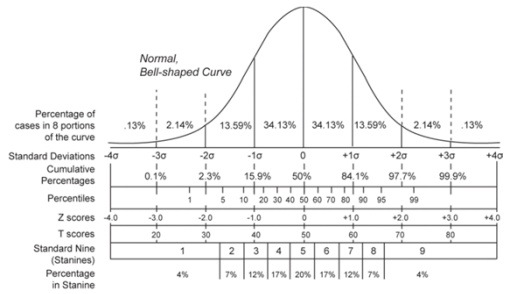
- Funding rules have not yet changed
- NIH is gathering comments from researchers
  - Which research areas need sex balance the most
  - What challenges scientists face in including male and female subjects in their studies
- The NIH is also making videos and online tutorials to teach scientists who are new to studying both sexes how to design such studies
- Details about the policy and implementation plans are expected to roll out during the next year

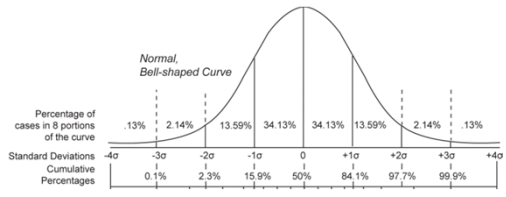




Z Score


The Normal Curve
Mean
68%
95%
99%
S.D. -1.96
-1.00
0
+1.00
+1.96


Normal,
Bell-shaped Curve
Percentage of cases in 8 portions of the curve
.13%
2.14%
13.59%
34.13%
34.13%
13.59%
2.14%
.13%
Standard Deviations
-4σ
-3σ
-2σ
-1σ
0
+1σ
+2σ
+3σ
+4σ
Cumulative Percentages
0.1%
2.3%
15.9%
50%
84.1%
97.7%
99.9%
Percentiles
1
5
10
20
30
40
50
60
70
80
90
95
99
Z scores
-4.0
-3.0
-2.0
-1.0
0
+1.0
+2.0
+3.0
+4.0
T scores
20
30
40
50
60
70
80
Standard Nine (Stanines)
1
2
3
4
5
6
7
8
9
Percentage in Stanine
4%
7%
12%
17%
20%
17%
12%
7%
4%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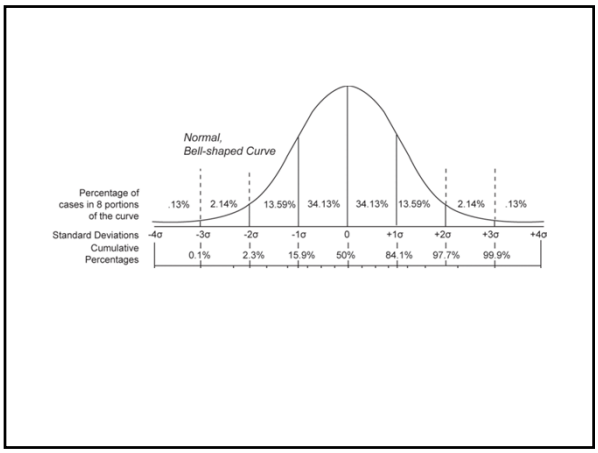
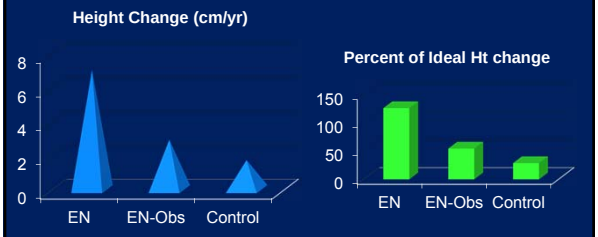
-3σ
-2σ
-1σ
0
+1σ
+2σ
+3σ
+4σ
Cumulative Percentages
0.1%
2.3%
15.9%
50%
84.1%
97.7%
99.9%



Monitoring

- Biologic parental ht for calculation of target ht
  - Females: [Mother's Ht (cm) + Father's Ht (cm) – 13]/2
  - Males: [Mother's Ht (cm) + Father's Ht (cm) + 13]/2
- 3rd percentile for target ht = target ht - 8.5 cm
- 97th percentile for target ht= target ht + 8.5 cm

Enteral Nutrition

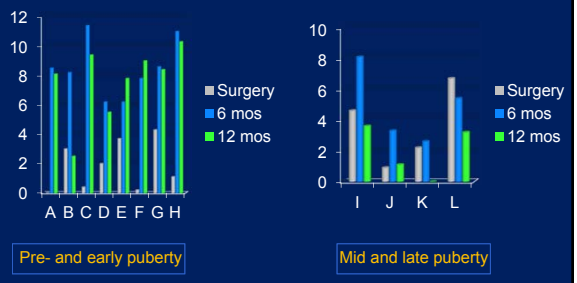


- P< .01 EN observational yr vs EN experimental yr
- P< .01 EN vs Controls (experimental yr)

Belli et al, Gastroenterology, 1988

Surgery

Height Velocities (cm/yr)



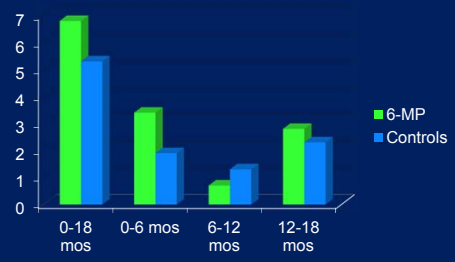
Pre- and early puberty

Mid and late puberty

Lipson et al, Eur J Pediatr, 1990

6-Mercaptopurine

Mean Linear Growth (cm)

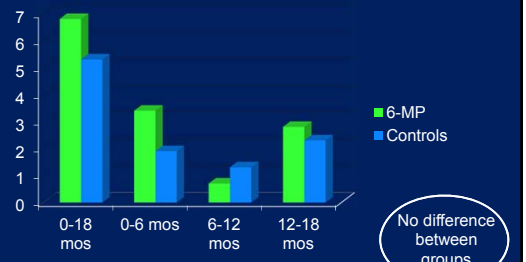


Study Time Period

Markowtiz et al, Gastroenterology, 2000

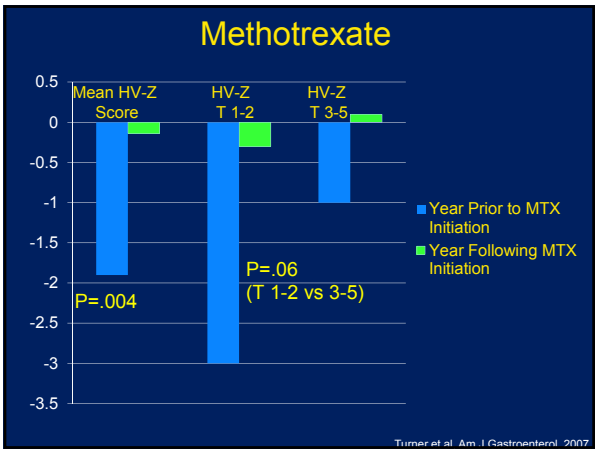
6-Mercaptopurine

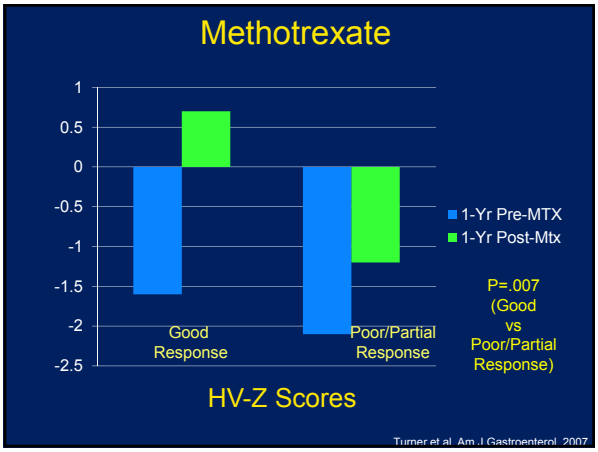
Mean Linear Growth (cm)

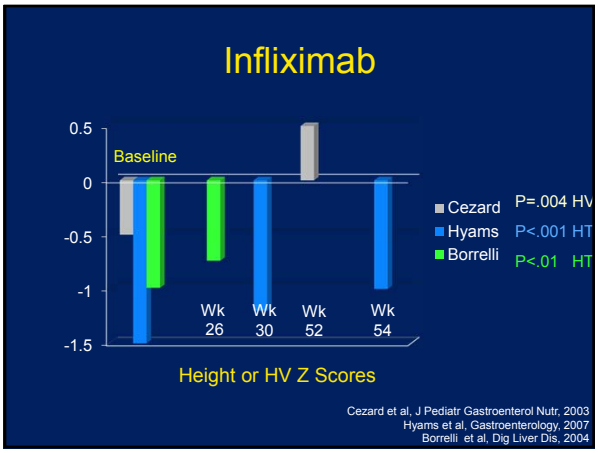


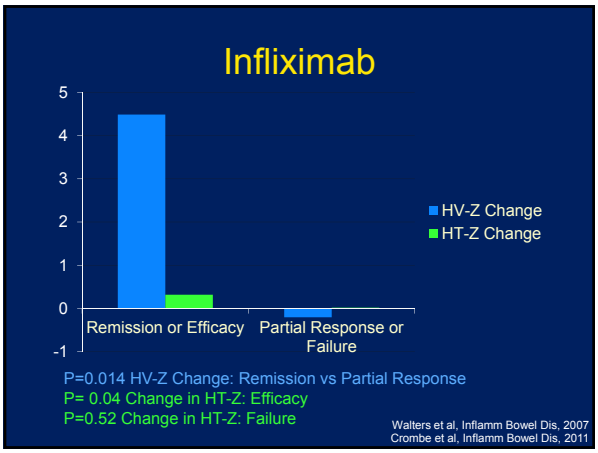
Study Time Period

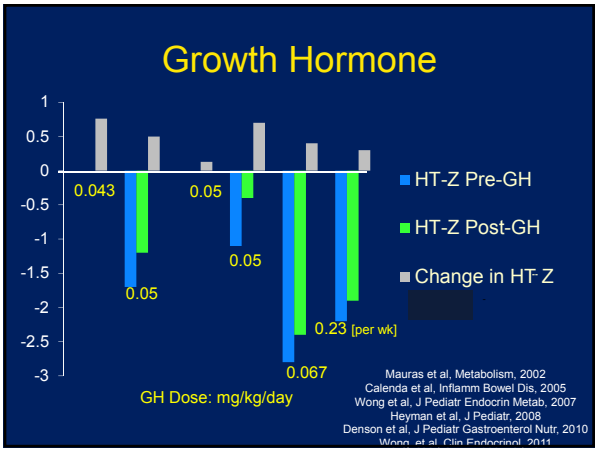
Markowtiz et al, Gastroenterology, 2000

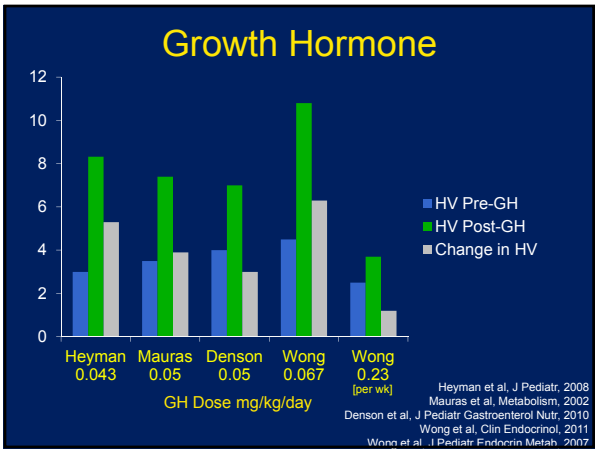

Methotrexate
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
Mean HV-Z Score
HV-Z T 1-2
HV-Z T 3-5
P=.004
P=.06
(T 1-2 vs 3-5)
Year Prior to MTX Initiation
Year Following MTX Initiation
Turner et al, Am J Gastroenterol, 2007

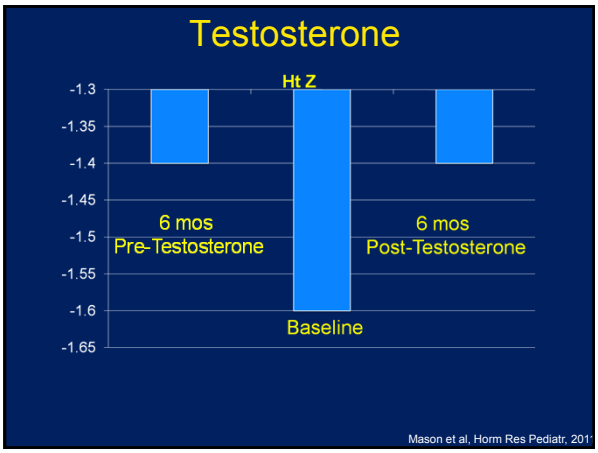

Methotrexate
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
Good Response
Poor/Partial Response
1-Yr Pre-MTX
1-Yr Post-Mtx
P=.007
(Good vs Poor/Partial Response)
HV-Z Scores
Turner et al, Am J Gastroenterol, 2007

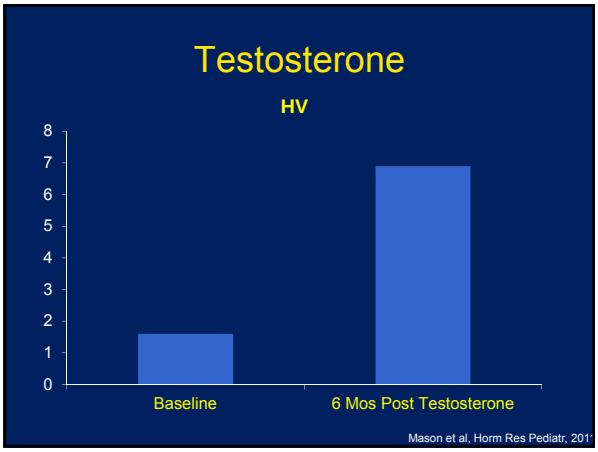

Infliximab
0.5
0
-0.5
-1
-1.5
Baseline
Wk 26
Wk 30
Wk 52
Wk 54
Cezard
Hyams
Borrelli
P=.004 HV
P<.001 HT
P<.01 HT
Height or HV Z Scores
Cezard et al, J Pediatr Gastroenterol Nutr, 2003
Hyams et al, Gastroenterology, 2007
Borrelli et al, Dig Liver Dis, 2004

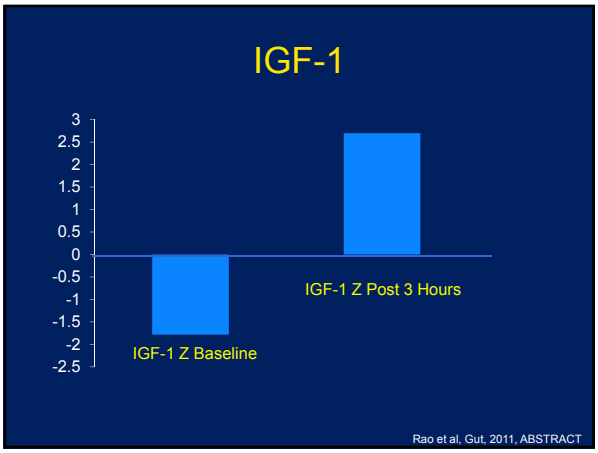

Infliximab
5
4
3
2
1
0
-1
HV-Z Change
HT-Z Change
Remission or Efficacy
Partial Response or Failure
P=0.014 HV-Z Change: Remission vs Partial Response
P= 0.04 Change in HT-Z: Efficacy
P=0.52 Change in HT-Z: Failure
Walters et al, Inflamm Bowel Dis, 2007
Crombe et al, Inflamm Bowel Dis, 2011


Growth Hormone
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
0.043
0.05
0.05
0.05
0.23 [per wk]
0.067
HT-Z Pre-GH
HT-Z Post-GH
Change in HT-Z
GH Dose: mg/kg/day
Mauras et al, Metabolism, 2002
Calenda et al, Inflamm Bowel Dis, 2005
Wong et al, J Pediatr Endocrin Metab, 2007
Heyman et al, J Pediatr, 2008
Denson et al, J Pediatr Gastroenterol Nutr, 2010

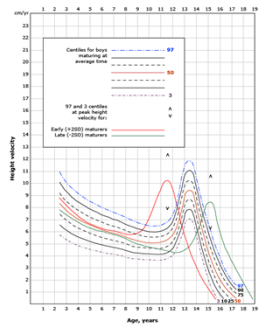

Growth Hormone
12
10
8
6
4
2
0
HV Pre-GH
HV Post-GH
Change in HV
Heyman 0.043
Mauras 0.05
Denson 0.05
Wong 0.067
Wong 0.23 [per wk]
GH Dose mg/kg/day
Heyman et al, J Pediatr, 2008
Mauras et al, Metabolism, 2002
Denson et al, J Pediatr Gastroenterol Nutr, 2010
Wong et al, Clin Endocrinol, 2011


Testosterone
Ht Z
-1.3
-1.35
-1.4
-1.45
-1.5
-1.55
-1.6
-1.65
6 mos
Pre-Testosterone
6 mos
Post-Testosterone
Baseline
Mason et al, Horm Res Pediatr, 201


Testosterone
HV
8
7
6
5
4
3
2
1
0
Baseline
6 Mos Post Testosterone
Mason et al, Horm Res Pediatr, 201


IGF-1
3
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
IGF-1 Z Post 3 Hours
IGF-1 Z Baseline
Rao et al, Gut, 2011, ABSTRACT

Height velocity in American boys



Height velocity by age for American boys. Red line: 50th centile for boys maturing 2 SD earlier than the mean; Green line: 50th centile for boys maturing 2 SD later than the mean. Other lines show the 3rd (purple) through 97th (blue) centiles for boys maturing at an average time.
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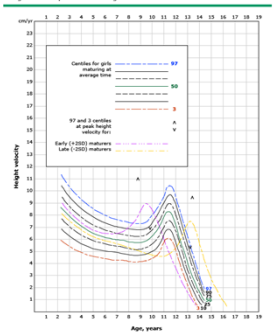
Height velocity in American girls



Height velocity by age for American girls. Purple line: 50th centile for girls maturing 2 SD earlier than the mean; Yellow line: 50th centile for girls maturing 2 SD later than the mean. Other lines show the 3rd (red) through 97th (blue) centiles for girls maturing at an average time.
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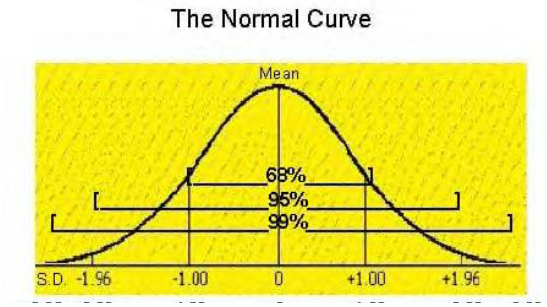
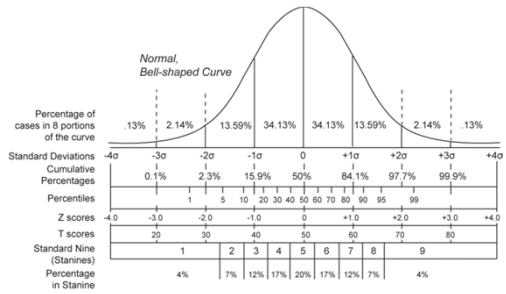
Z Score





Monitoring

- Biologic parental ht for calculation of target ht
  - Females: [Mother's Ht (cm) + Father's Ht (cm) – 13]/2
  - Males: [Mother's Ht (cm) + Father's Ht (cm) + 13]/2
- 3rd percentile for target ht = target ht - 8.5 cm
- 97th percentile for target ht= target ht + 8.5 cm

Growth Study

Growth Impairment Definitions for Our Study

- Height Velocity Z Score < -1.66
- Change in Height Velocity Z score of -0.5 from the screening visit
- Height Z Score < -1.66

Z Scores Based on Bone Age

Bone Age