Pediatric Endocrinology Post ENDO

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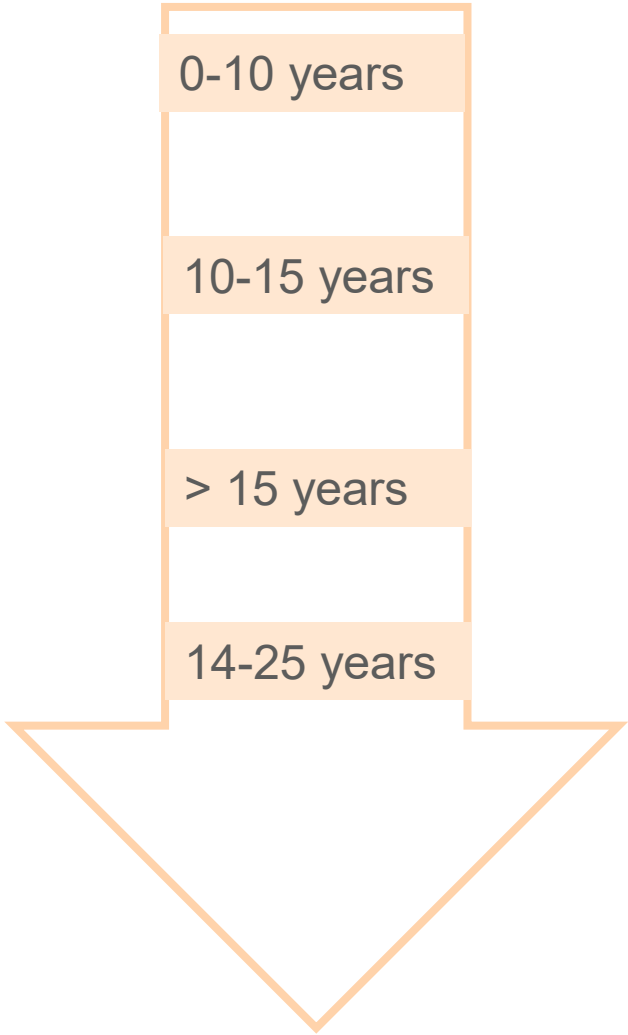
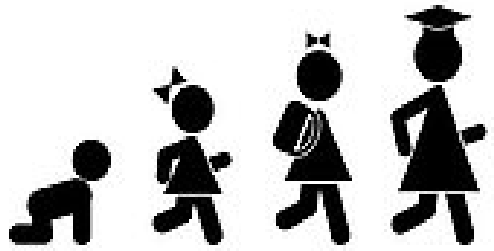
PostENDO Symposium 1. September 2022, Bern

A journey through childhood and adolescence to the transition into adulthood

Outline

- Disorders in pubertal development
- Approach to fractures in children
- Primary ovarian insufficiency
- Transition - diabetes





Disorders of precocious pubertal development

- Meet the professor: Precocious Puberty: Evidence Based Management
  Dr Maria Vogiatzi

- Symposium: Disorders of pubertal development
  Prof Anders Juul

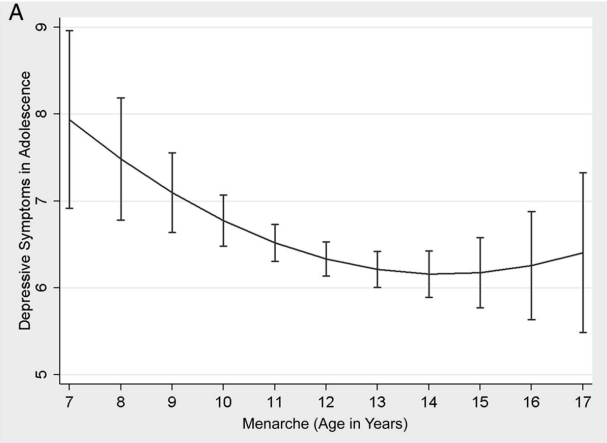
Precocious puberty

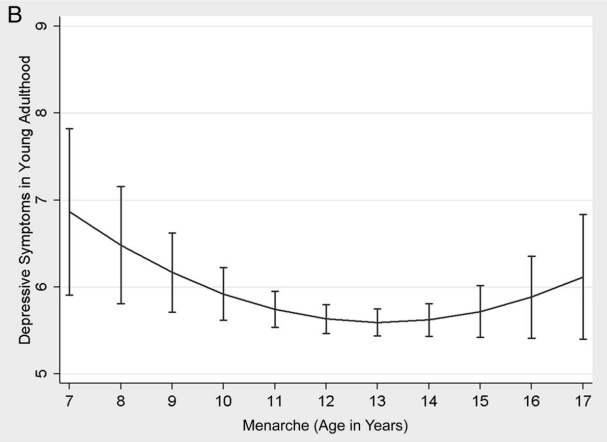
- Definition
  - Onset of clinical signs of puberty before ♀ Age 8 years
    ♂ Age 9 years
- Best test to diagnose central precocious puberty: baseline LH measurement

	Sensitivity, %	Specificity, %	Formulation	Subjects, *n* (sex)	Method	Study
Unstimulated LH (IU/L)						
>0.3	77	100	–	49 (F)	ICMA	Neely et al. [7]
<0.3 (prepubertal) >0.83 (clearly pubertal) >0.3 but <0.83 (overlap of prepubertal and pubertal)	93	100		25 (F)	ICMA	Houk et al. [8]
<0.2 (prepubertal) >0.2 (pubertal)	91	100		59 (F)	ICMA	Harrington et al. [10]

Krishna et al. Horm Res Paediatr. 2019;91(6):357-372

Psychosocial burden



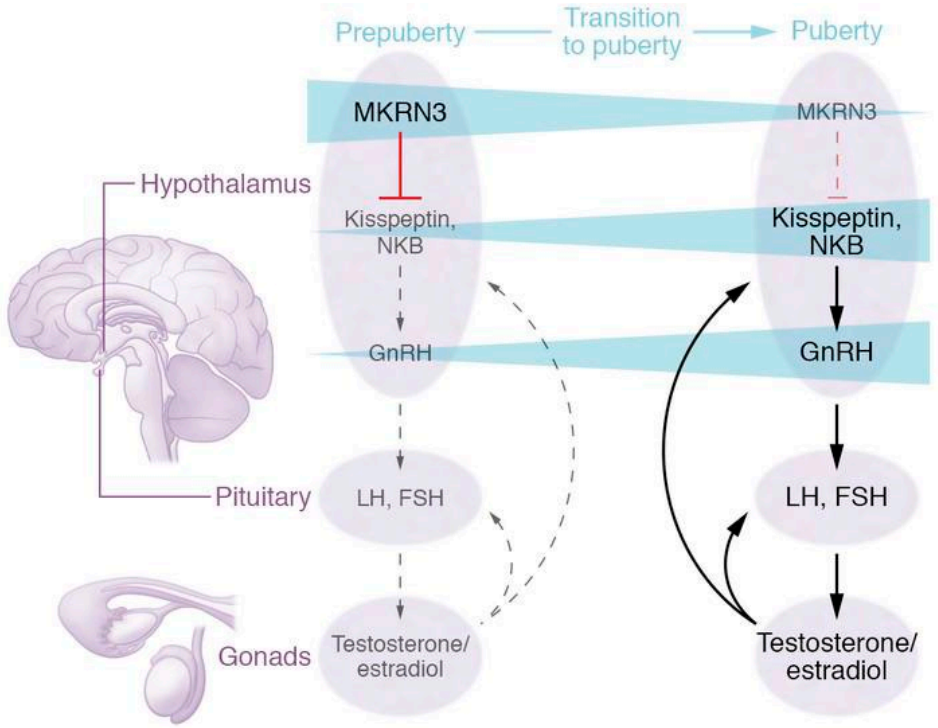


Earlier age at menarche → higher rates of depression & anti-social behavior [1, 2]

No strong data comparing psychosocial assessements pre, during and post GnRHa treatment [3]

[1] Mendle et al. Pediatrics. 2018;141(1). [2] Mendle et al. J Adolescent Health. 2019 Nov;65(5):599-606
[3] Williams VSL et al. J Pediatr Endocrinol Metab 2018; 31(5):485-495

Genetics of central precocious puberty

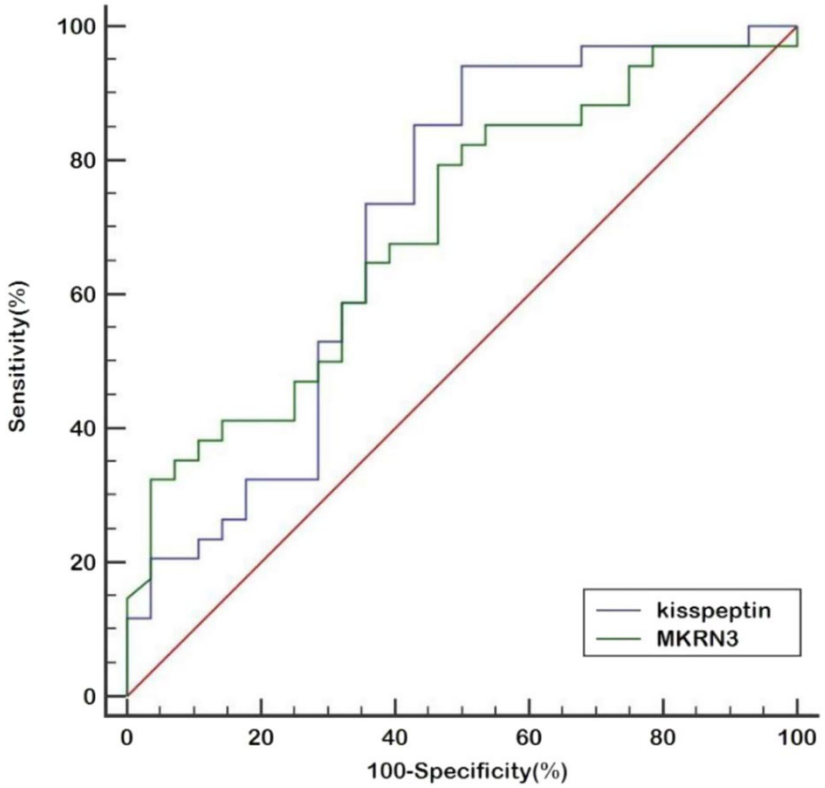


- Makorin ring finger protein 3 (MKRN3) variants in persons with central precocious puberty:
  - Pooled: 9%
  - Around 19 % (up to 46%) in familial forms
- Kisspeptin (KISS1), kisspeptin receptor (KISS1R) and delta-like homolog 1 (DLK1) variants are rare

Abbara A et al, Journal of Clinical Investigation 2020 Aug 3;130(8):3957-3960

Valadares LP et al. J Endocr Soc. 2019 Mar 25;3(5):979-995
Schneider Aguirre R et al. Best Pract Res Clin Endocrinol Metab. 2018;32(4):343-354

Serum levels of kisspeptin and MKRN3

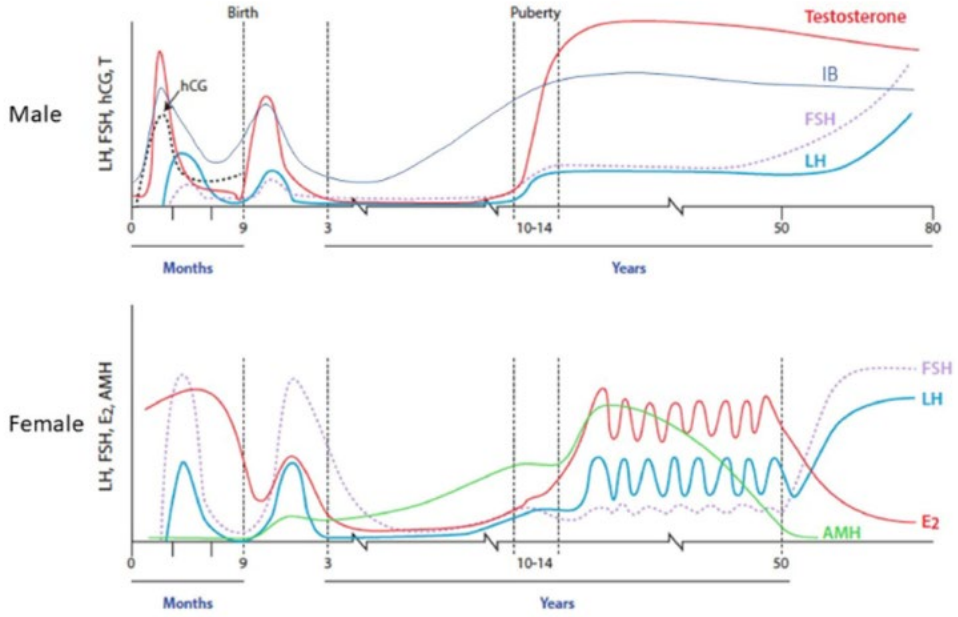


Differentiation between central precocious puberty and premature thelarche and prepubertal status not possible

Li M, Endocr Connect. 2021 Sep 20;10(9):1147-1154.

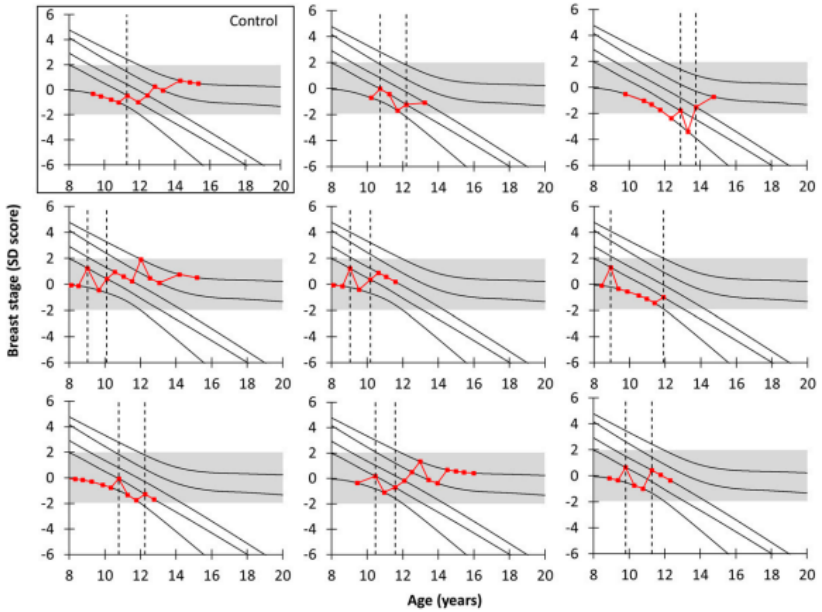
Transient thelarche

- In minipuberty 25% of boys and girls present with transient thelarche



Howard S. Clin Endo 2021;95:702–715.

- In puberty, 8-12% of girls present with transient thelarche
- in 50% first sign is pubarche



Lindhardt Jihansen M et al., JCEM 2019, 102(3):1001–1008
Soto et al. Clin Endo, 2020 Sep;93(3):296-304.

Approach to Fractures in Childhood

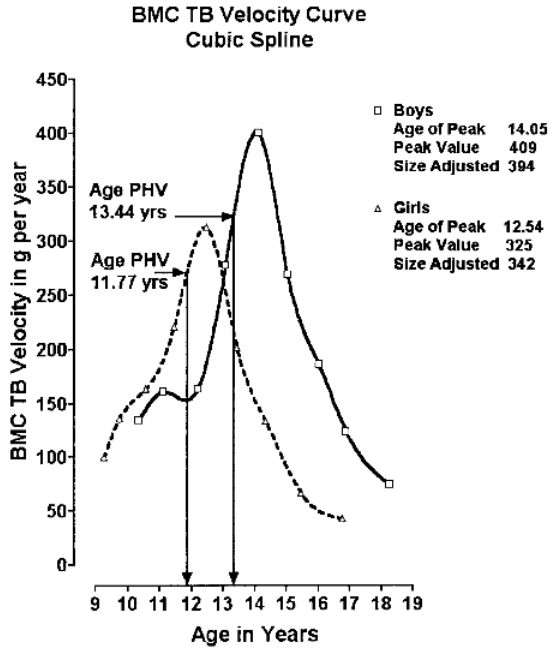
Meet the professor: Approach to fractures in children

Rachel Gafni

Some facts

- Bone fractures during childhood are common and peak between 11 and 15 years
- Peak skeletal maturation lags behind peak skeletal growth

- Indications for bone mineral density:
  - Clinically significant fracture history:
    - Vertebral compression fracture
    - 2 or more long bone fractures before the age of 10 years
    - 3 or more long bone fractures before the age of 19 years
  - Medical conditions / therapies associated with low bone density



Hedstrom et al., Acta Orthopaedica 2010; Farr et al. Natur Rev Endocrinology 2015; Gordon et al, J Clin Densitometry 2014; Bailey et al. JBMR 1999

Challenges with bone mineral density (BMD)

- Areal BMD is highly affected by bone size:
  - Patients with short stature for age may have artifactually low aBMD
  - Patients with tall stature for age may have artifactually high aBMD

    → use of height adjusted z-score
- BMD Z-score between –2 and +2 SD is considered to be within the normal range
- Correlation between BMD and fracture risk in children is not well-established
  - particularly in children with chronic diseases

    → the diagnosis of osteoporosis is not based on DXA alone, it is a clinical diagnosis

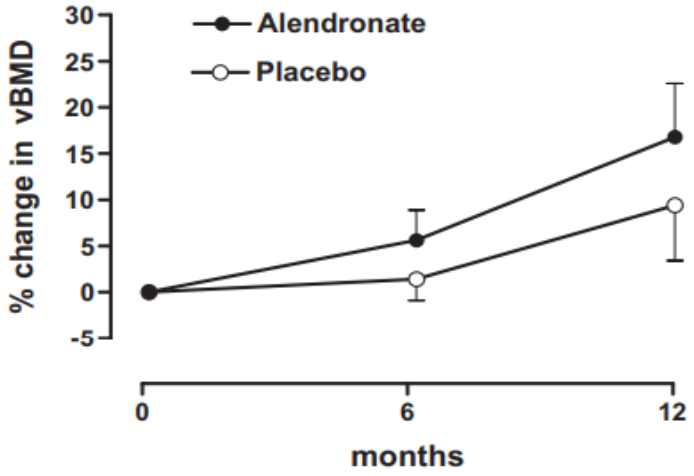
Gordon CM; International Society for Clinical Densitometry. 2013 Pediatric Position Development Conference: executive summary and reflections. J Clin Densitom. 2014;17(2):219-224.

Treatment

- Treat underlying cause
- Optimize general nutrition
- Calcium and Vitamin D
- Encourage weight-bearing
- Consider bisphosphonates if treatment unsuccessful and the child/adolescent is actively fracturing

Bisphosphonates

- Aledronate in children on glucocorticoids
- Zoledronate for Crohns Disease



Rudge et al. Rheumatology 2005 Jun;44(6):813-8.

Table 2 Bone mineral density scores

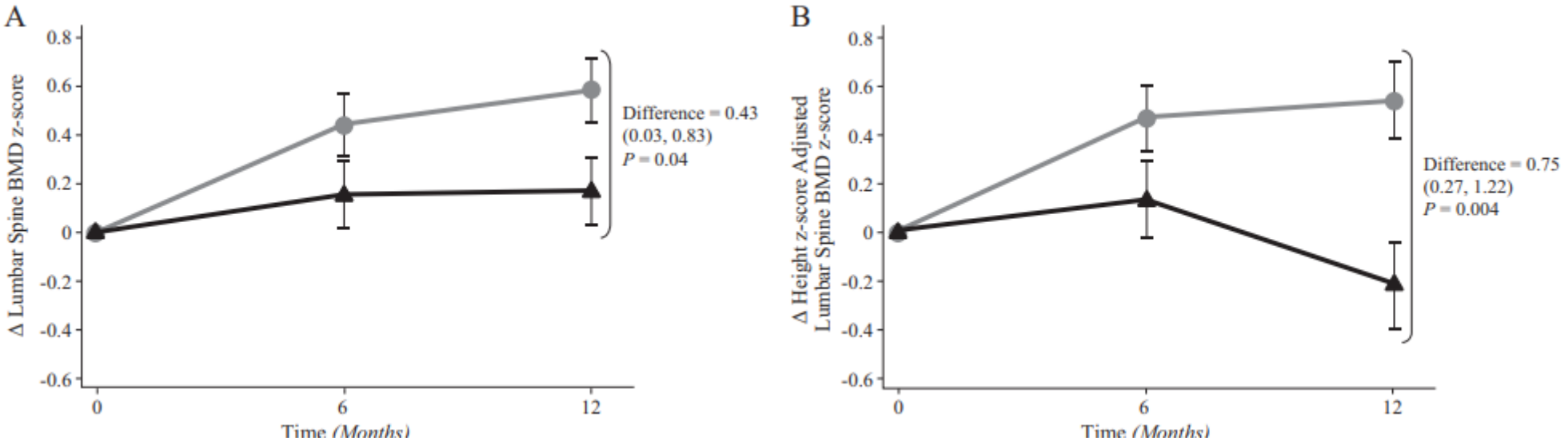
	Zoledronic acid ($n = 7$)			Placebo ($n = 6$)		
	Baseline	6 months	12 months	Baseline	6 months	12 months
LSBMDZ	–2.3 (–2.6– –2.2)	–1.6 (–0.8– –2.3)*	–1.5 (–2.0– –0.8)†	–2.7 (–3.3– –1.9)	–2.6 (–3.2– –1.8)	–2.3 (–3.3– –1.4)‡
LSvBMDZ	–2.2 (–2.7– –1.3)	–1.1 (–2.0–0.0)*	–1.4 (–2.0– –0.1)†	–2.7 (–3.5– –2.1)	–2.4 (–3.5– –0.9)	–2.3 (–3.5– –0.9)‡
TBBMDZ	–1.1 (–2.2–0.2)	ND	–0.9 (–1.8–0.6)	–1.9 (–2.1–0)	ND	–1.6 (–2.4– –0.1)

LSBMDZ, lumbar spine bone mineral density Z-score; LSvBMDZ, volumetric LSBMDZ; TBBMDZ, total body bone mineral density Z-score. Values represent mean and range.
*$P < 0.001$ for ΔLSBMDZ and ΔLSvBMDZ at 6 months (unpaired t-test).
†$P = 0.02$ for ΔLSBMDZ and ΔLSvBMDZ at 12 months in treated group (repeated measures ANOVA).
‡$P = 0.047$ for ΔLSBMDZ and ΔLSvBMDZ at 12 months in placebo group (repeated measures ANOVA).
ND, Not done.

Sbrocci et al. . 2010 Oct;52(5):754-61

Zoledronate in Pediatric Glucocorticoid-induced Osteoporosis

- Double-blind, placebo controlled
- N=34, GIO and vertebral fracture
- Zoledronate vs placebo every 6 months



Ward et al. JCEM 2021 Nov 19;106(12):e5222-e5235.

Primary ovarian insufficiency

Meet the professor: The Adolescent with Primary Ovarian Insufficiency: Protecting Long-Term Health - Management Strategies for Primary Ovarian Insufficiency in Adolescence

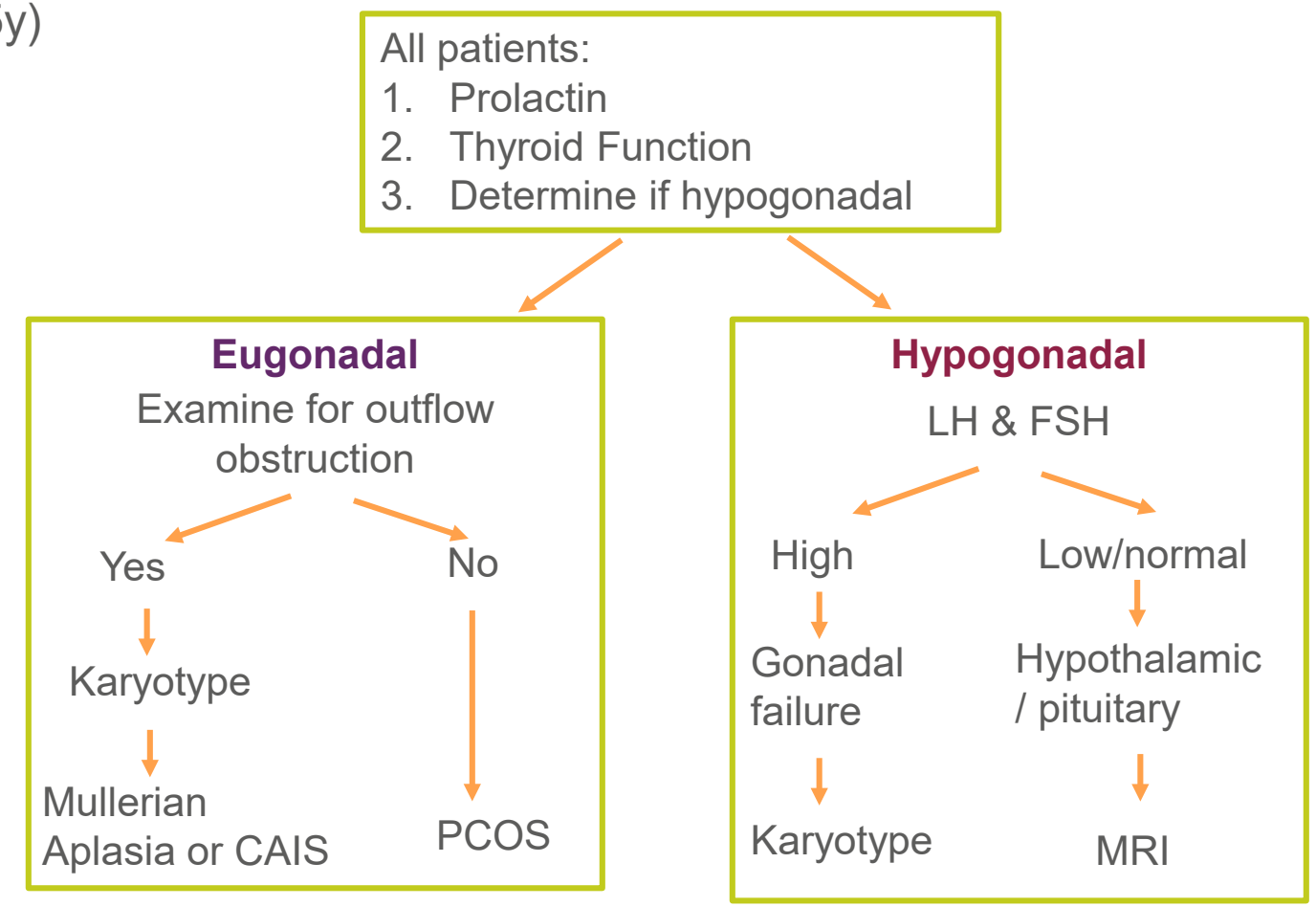
Dr Lawrence Layman

Primary ovarian insufficiency – some facts

- Occurence 1-3%
- Definition:
  - 3-6 months of hypoestrogenic amenorrhea < age 40
  - elevated gonadotropins at least twice 4 weeks apart
- Prior to puberty – during puberty – after puberty
- Pay attention to pubertal development & stature
- Etiologies:
  - Chromosomal: most common: Turner Syndrome (including mosaicism)
  - Genetic
  - Autoimmune
  - Chemotherapy & radiation

Diagnostic approach in adolescence

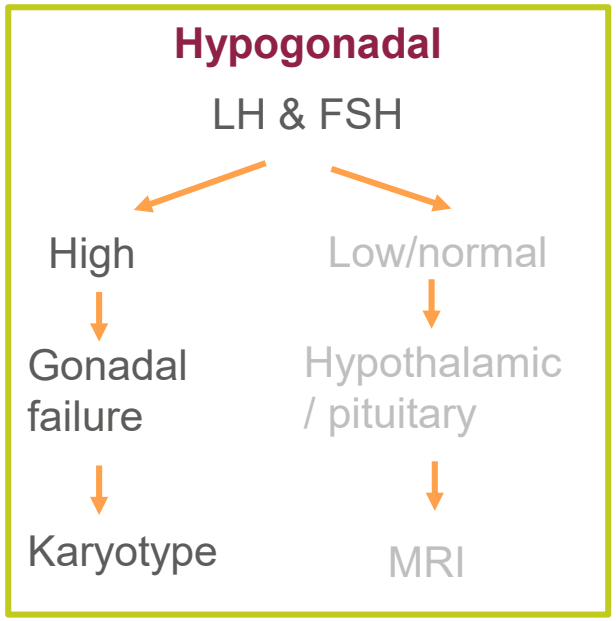
- Amenorrhea ≥ 3-6 months and delayed puberty (no breast development by age of 13 and no menarche by the age of 15y)



Adapted form Layman and Reindollar Adolesc Med. 1994 Feb;5(1):37-56

46,XX Primary Ovarian Insufficiency

- Autoimmune disease:
  - Autoimmune thyroiditis
  - Addison disease
  - Type 1 diabetes
- Genetic testing:
  - Fragile X syndrome testing
  - Targeted POI gene panel can be considered



Stuenkel CA et al, JCEM, 2022, 107 (3), 825–835,

FMR1 Gene

- Gene involved in Fragile X syndrome: X-linked dominant disorder with reduced penetrance
- Due to full expansion of triplet CGG repeat in the FMR1 gene:
  - Normal 5-50 repeats
  - Premutation 50-200 repeats: RNA overexpression mechanism
  - Full mutation > 200 repeats: methylation of the promoter and gene is inactivated
- Different Phenotypes

Full mutation

Males

- Intellectual disability/autism
- facial abnormalities
- macroorchidism

Females

- Can have Intellectual disability (less severe, no POI)

Premutation

Males

- 20% risk of tremor / ataxia

Females

- Known Fragile X families: 15-20% POI risk
- If done because of POI 3-4%, 10-15% if ≥ 2 fam members with POI
- 15% risk of tremor ataxia

McGlacken-Byrne SM, Best Pract Res Clin Obstet Gynaecol. 2022 May;81:98-110

Management of POI

- Oral or transdermal estrogen treatment: complete pubertal development, prevent osteoporois and cardiovascular disease
- Add progestin once pubertal development completed or occurence of vaginal bledding
- Treat until age of menopause
- Does not pose the same risks as menopausal hormone replacement given for menopause
- FMR1 status can be useul even if pregnancy is not possible
- Yearly assessment for thyroid, adrenal, diabetes

Stuenkel CA et al, JCEM, 2022, 107 (3), 825–835,

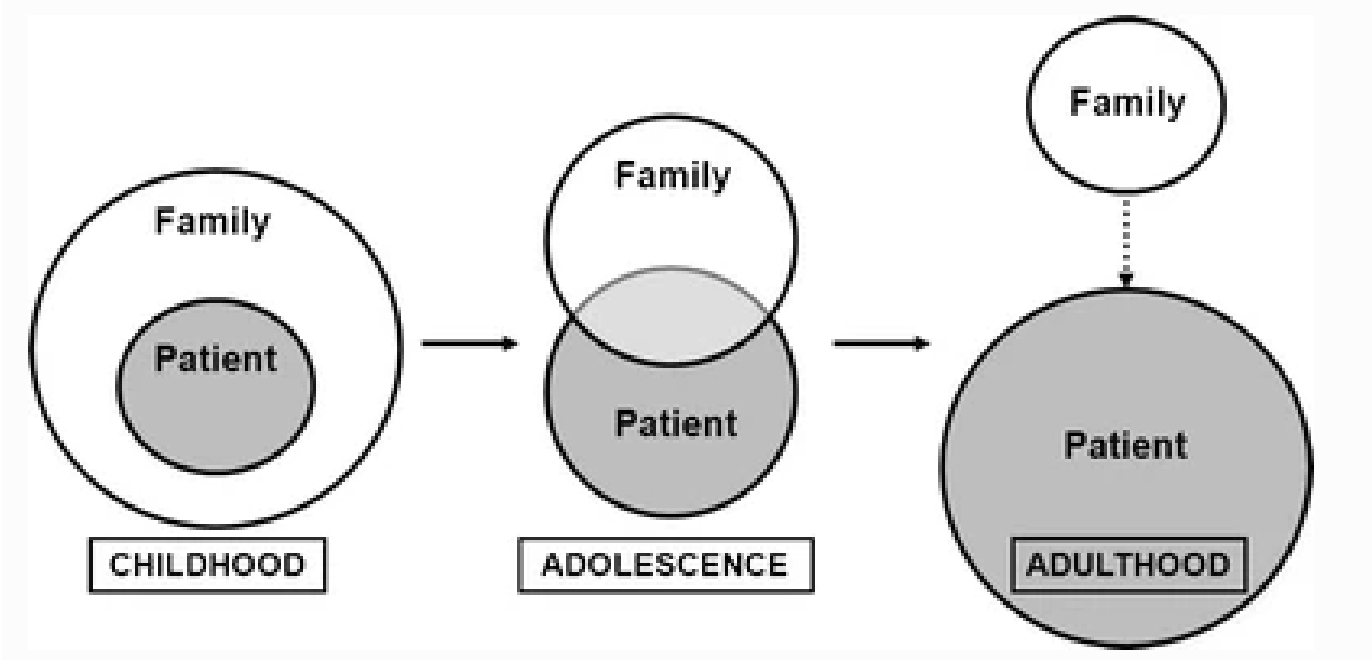
Transition – diabetes

Symposium: Transitions in Care From Pediatric to Adult Endocrinology

Dr Shiwani Agarwal

What is transition

- Process of moving from child to adult model of health care with or without transfer to a new healthcare provider



White and Cooley, Pediatrics. 2018 Nov;142(5):e20182587
Garvey, Laffel et al. Curr Diab Rep. 2012 Oct;12(5):533-41.

Transition is a process

Gottransition.org.

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Associated factors for successful transition

Table 2—Factors associated with a gap of >6 months in care between pediatric and adult providers

	Total *N* (%)	Gap in care >6 months *n* (%)	OR (95% CI)[a]
No. of visits to pediatric provider during 12 months before transition			
0–2 visits	101 (36)	32 (32)	3.2 (1.7, 6.1)
≥3 visits	183 (64)	25 (14)	1.0
Participant-reported preparedness to transition[b]			
Prepared	197 (66)	29 (15)	1.0
Not prepared	102 (34)	34 (33)	3.3 (1.7, 6.3)

Garvey et al. Diabetes Care 2017;40:317–324 .

Barriers to transition

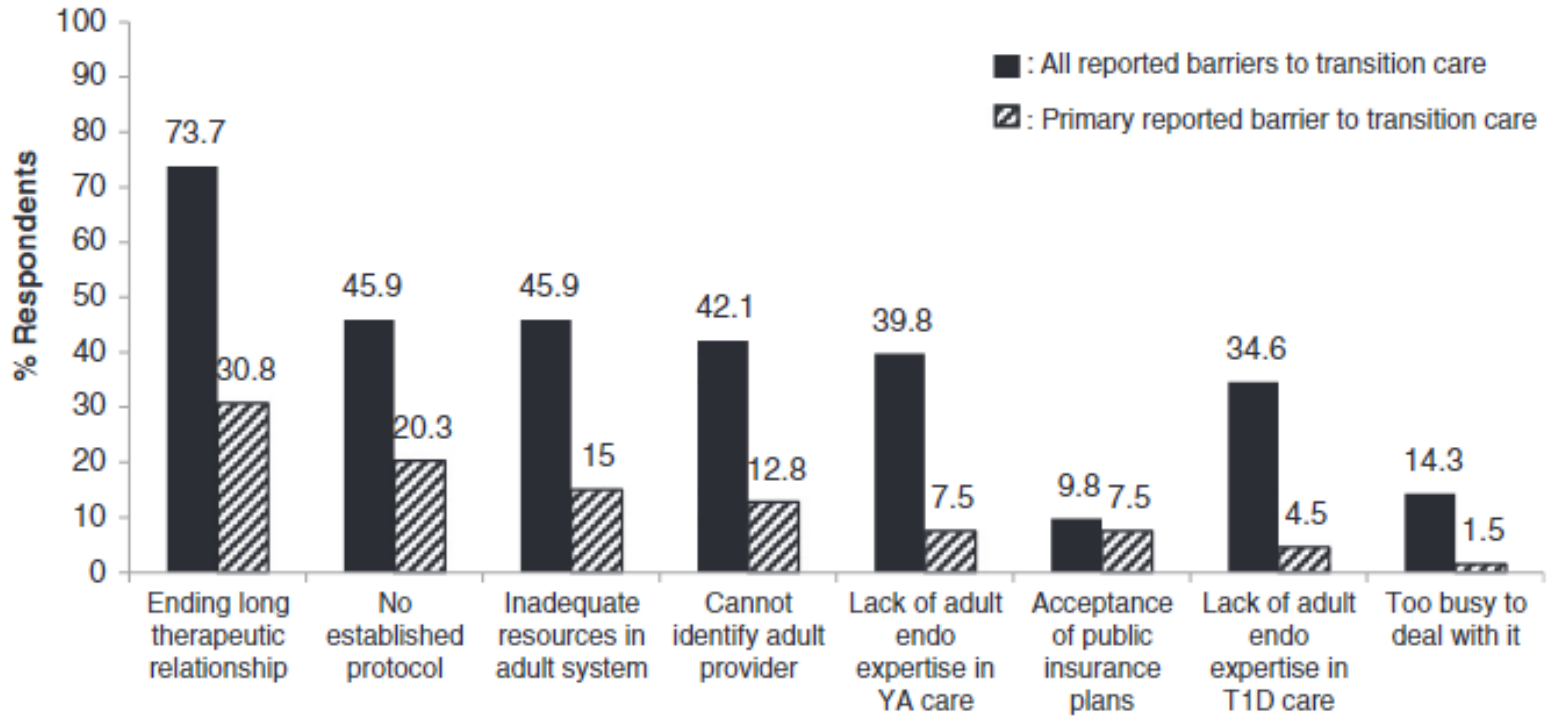


FIGURE 2 Barriers to transition care

Agarwal et al. Pediatric Diabetes 2017 Nov;18(7):524-531.

Transition in type 1 diabetes – transition readiness

Development and Implementation of the Readiness Assessment of Emerging Adults With Type 1 Diabetes Diagnosed in Youth (READDY) Tool

Sarah D. Corathers,[1] Joyce P. Yi-Frazier,[2] Jessica C. Kichler,[3] Lisa K. Gilliam,[4] Gail Watts,[2] Andrea Houchen, and Sarah Beal[3]

[1]Division of Endocrinology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH; [2]Department of Pediatrics, Seattl Children's Hospital, Seattle, WA; [3]Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, University Cincinnati, Cincinnati, OH; [4]Kaiser Northern California Diabetes Program, The Permanente Medical Group South San Francisco Medical Center, Sa Francisco, CA

› Diabetes Spectr. 2022 Feb 15;35(1):57-65. doi: 10.2337/ds20-0104. Epub 2022 Feb 8.

Opportunities for Enhanced Transition of Care Preparation for Adolescents and Emerging Adults With Type 1 Diabetes: Use of the READDY Transition Tool

Camilia Kamoun [1], Jane C Khoury [2 3 4 5], Sarah J Beal [5 6], Nancy Crimmins [2 5], Sarah D Corathers [2 5]

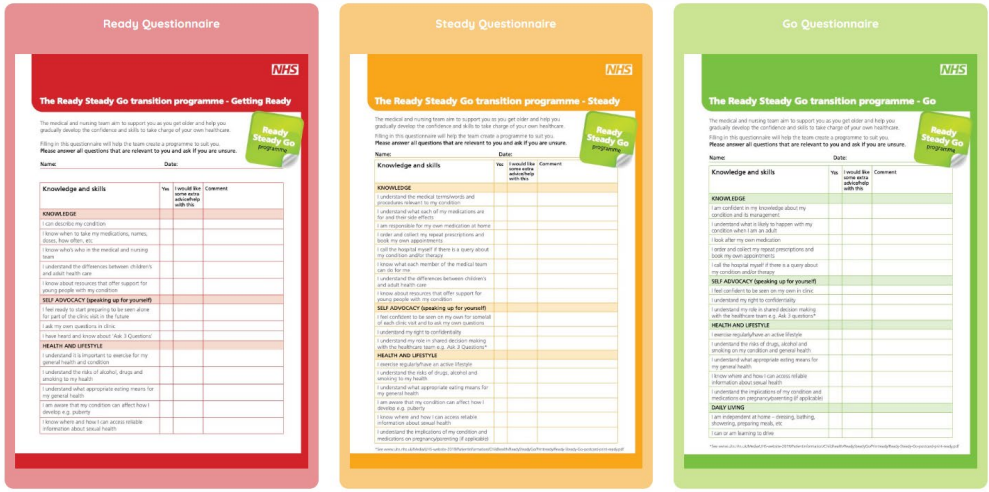
- Domains: Diabetes Knowledge, Healthcare System Navigation, Insulin Self Management, Health Behaviors
- Doctor counseling was associated in higher confidence level

Toolkits

Transitions of Care

A Successful Approach to Managing Pediatric to Adult Transitions of Care

Transitioning from a pediatric to an adult provider can be a challenge for all members of the care team. Transitions toolkits have been developed for **Type 1 Diabetes**, **Growth Hormone Deficiency**, **Turner Syndrome** and **Transgender Health** to help ease this transition.



https://www.endocrine.org/improving-practice/transitions

https://www.readysteadygo.net/

Take home messages….

…. Post Endocrine from early childhood through puberty and adolescence

- Precocious puberty: genetics play a role
- Fractures: Bisphosponate treament in children with GIO is successful
- Primary ovarian insufficiency: Turner, autoimmunity and FMR1 gene
- Transition programs and readiness are important

Thank you for your attention!

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