Glance at Puberty: from premature adrenarche to central precocious puberty

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Disclosure

- I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Goals

- Distinguish between the variations of normal (eg, thelarche, pubarche) and precocious puberty.
- Recognize the signs and symptoms of precocious puberty. Know the differential diagnosis of precocious puberty. Recognize the importance of obtaining the history of medication use.
- Know how to use laboratory tests effectively to distinguish an adrenal etiology of precocious puberty.
- Know the work up done for precocious puberty
- Know the management of precocious puberty .

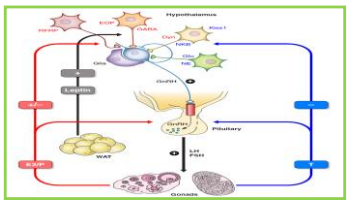
Hypothalamic- Pituitary- Gonadal axis

- The HPG axis is functional around 20 weeks of gestation.
- After birth, withdrawal from maternal estrogens causes an increase in gonadotropins, which leads to a physiologic "mini-puberty"
- Gonadotropin secretion then returns to minimal levels, until production is stimulated by the GnRH pulse generator during puberty.

Physiology of Puberty

- The onset of puberty is triggered by increased pulsatile release of GnRH from the hypothalamus.
- Release of GnRH leads to secretion of gonadotropins, LH and FSH, from the pituitary gland
- LH and FSH then stimulate the enlargement of the gonads and production of sex steroids

Hypothalamic-Pituitary-Gonadal Axis



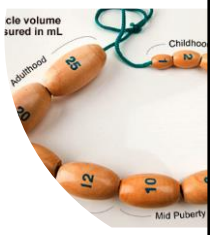
Pinella L et al Physiol Rev 2012

Puberty terminology

- Thelarche
  - Onset of female breast development
- Pubarche
  - Onset of pubic hair development
- Adrenarche
  - Onset of signs of adrenal androgen production
    - Adult body odor, acne, axillary hair, pubic hair
- Gonadarche
  - Onset of enlargement of the gonads (ovaries/testes) and production of sex steroids

Assessment of Puberty

- Assessment of pubertal development is described by Tanner Staging (Sexual Maturity Rating)
- Assessment of breast development should be done by palpation, not simply inspection.
- Testicular size determined using an orchidometer (volume) or measuring the longitudinal axis.
- Physical exam can also provide clues about hormonal origins
  - Vaginal mucosa- shiny, red→ Unestrogenized
    - Pink→ Estrogenized
  - Testicular size- enlarged→ Gonadotropin activation
    - Pre-pubertal- Adrenal source of androgens



Tanner Stage	Breasts	Pubic Hair	Testicular Volume
I	Pre-pubertal	Pre-pubertal	≤ 3mL
II	Breast buds (Enlarged areolae, palpable and visible elevated contour)	Minimal pigmented hair (primarily on the labia or at the base of the penis) "Can count"	4-6 mL
III	Breast tissue extends beyond the areolae, incomplete nipple development	Coarser and more numerous hair extending to mons pubis "Too many to count"	6-10 mL
IV	Secondary mound of areola and papilla	Hair is dense and continuous but does not extend to medial thighs	10-15 mL
V	Adult	Adult (Extends to medial thighs)	>15 mL

Puberty-Girls

- In females, the first sign of puberty is typically thelarche
  - 20% of girls may present with pubarche
- On average, menarche occurs 2 years after the onset of breast development.
  - Early breast development → longer interval
  - Late breast development → shorter interval
- Growth spurt occurs during Tanner II-III
- Duration of puberty is on average 3-4 years

Puberty-Boys

- Testicular enlargement is usually the first sign of pubertal development.
- Boys also have accompanying hair growth in androgen-sensitive areas (face, chest, back, abdomen, and upper thighs)
  - Thickness and distribution of hair is affected by ethnic and familial factors more than androgen levels
- Gynecomastia can occur normally during puberty (up to 2/3 of boys)
  - Self-limited and will usually regress within 1-2 years
- Growth spurt occurs during Tanner III-V
- Duration of puberty is on average 3-4 years.

Timing in Puberty

- Normal timing for pubertal onset:
  - Girls: 8-13 years
  - Boys: 9-14 years
- There is some controversy concerning if normal timing for pubertal onset varies among races.

Timing in puberty

Table 1.– Reported recent age ± SD (years) for female sexual maturation in the UK and the USA

	Number of subjects (age range in years)	Breasts at Tanner stage 3	Menarche	Pubic hair at Tanner stage 3	Comments
Marshall and Tanner (UK) (1969)[7]	192 (8-19)	11.15 ± 0.18	13.47 ± 0.92	11.6 ± 3.1	Photographs, Whites
Reynolds and Wilson (USA) (1948)[8]	69 (8-16)	10.6 ± 1.3	12.9 ± 1.4	11.6 ± 3.1	Direct examination + photographs. Race (ref. data)
Nicolson and Hanby (USA) (1933)[9]	192	10.6	12.8	11.6	
Tanner et al. (UK) (1966)[10]	200 (6.0-17.0)	10.6 ± 2.6	13.0 ± 1.3	11.9 ± 1.5	Direct examination. Almost all whites
Billewicz et al. (UK) (1980)[11]	786 (9-17)	10.6 ± 2.6	13.4 ± 1.1		Direct examination. Whites
Backe et al. (USA) (1995)[12]	67 (8.2-17)	11.2 ± 0.7		11.6 ± 1.3	Whites. Assisted self-examination
Herman-Giddens et al. (USA) (1997)[13] (1996 study)	17,077 (3-12)	African-Americans 9.87 ± 2.42 Whites 9.96 ± 1.81	African-Americans 12.10 ± 1.21 Whites 12.88 ± 1.28	African-Americans 8.78 ± 2.0 Whites 10.16 ± 2.07	Only 94% African-Americans. Breast development assessed by palpation in 10% of girls. Otherwise by inspection
Sun et al. (USA) (2002)[14]	5253 (6-18)	African-Americans 9.40 Whites 10.18		African-Americans 9.67 Whites 10.67	Direct examination
Wu et al. (USA) (2002)[15]	1625 (<168 (8-16))	African-Americans 9.5 Whites 10.3	African-Americans 12.3 Whites 12.6	African-Americans 9.0 Whites 10.6	Direct examination
Freedman et al. (USA) (2002)[16] Data collected 1973-1976	1398 (7-16)		African-Americans 12.9 Whites 12.7		
Data collected 1992-1994	1120 (7-16)		African-American 12.1 Whites 12.5		
Chumlea et al. (USA) (2003)[17]	2359 (6-20)		African-American 12.06 Whites 12.59		
Anderson et al. (USA) (2003)[18] Data collected 1963-1970	1580 (10-12)		African-Americans 12.48 Whites 12.8		
Data collected 1988-1994	767 (10-13)		African-Americans 12.14 Whites 12.60		

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Importance of time of Puberty

- Precocious puberty may represent signs of a larger pathologic process
- May warrant further investigation into etiology.
- Developmental capacity for hygiene (ie. Menses)
- Possible risk for sexual abuse

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Importance of Timing of Puberty

- Potential negative psychological consequences of CPP are often used to justify treatment
- Considerations include risk for emotional distress and problem behavior
- Conclusions from existing studies inconsistent
- No firm recommendations for or against therapy are possible related to psychological outcomes at the present time

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Early Puberty

- **Sixty-two subjects aged 7.5 ± 1.4 years, (4.8-10.5)**
  - **19 with CPP, 22 with premature adrenarche (PA), 21 with early normal puberty (ENP)**
- **Psych measures: parent report, child self report and parent report of anxiety, depression & stress**
  - **no group differences were found for any child measure of psychological adjustment**
- **Mothers of girls with PA scored significantly higher than mothers of girls with ENP on one measure of depression (p = .04) and stress (p = .01)**

Psychological assessment of mothers and their daughters at the time of diagnosis of precocious puberty

Melissa J Schoelwer[1], Kelly L Donohue[2], Kristina Bryk[2], Paula Dobrich[2], Sheri A Berenbaum[3] and Erica A Eugster[1]

International Journal of Pediatric Endocrinology (2015)

	CPP n=15	PA n=8	ENP n=13
Age (mean years ± SD)			
Baseline[a]	7.31 ± 0.72	6.88 ± 0.89	8.71 ± 1.33
Follow-up[a]	8.36 ± 0.74	8.03 ± 0.66	9.72 ± 1.34
Race (% non-Caucasian)[b]			
	5 (33%)	5 (63%)	7 (54%)
BMI (mean z-score ± SD)			
Baseline[c]	1.33 ± 0.59	1.54 ± 0.98	1.22 ± 0.51
Follow-up	1.42 ± 0.59	1.57 ± 1.06	1.46 ± 0.42
Post-menarchal (%)			
Baseline	1 (7%)	0	4 (31%)
Follow-up	1 (7%)	0	5 (39%)

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Case discussion

- **A previously healthy 7-year-old girl presents for evaluation of precocious puberty.**
- **Parents report breast development for ~10 months along with adult body odor and rapid growth.**
- **Family history is significant for a half-sister on the paternal side who had menarche at age 7.**
- **On PE, height is at the 55th %tile and weight is at the 90th. Breasts are Tanner stage IV and pubic hair is Tanner stage II.**
- **A bone age x-ray is 12 years.**

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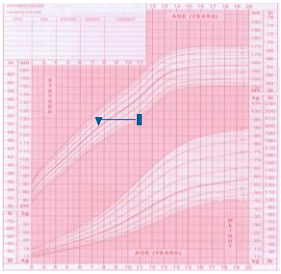

PAH-~55-56inches

Estradiol-34 pg/ml (<20)
US LH-0.250 mIU/ml (<0.3)

GnRHa stimulation test:

Peak LH-20 mIU/L (~4-6)
Estradiol-426 pg/ml

Differential Diagnosis of Precocious Puberty

- Central (Gonadotropin-dependent)
  - Idiopathic
  - International adoption
  - Intracranial tumor
  - Congenital brain anomaly
  - Infections
  - Intracranial irradiation
  - Trauma
  - Ischemia/ hemorrhage

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Differential Diagnosis of Precocious Puberty

- Peripheral and gonadal steroid- dependent (Gonadotropin-independent)
  - McCune-Albright Syndrome
  - Familial Male-Limited Precocious Puberty (Testotoxicosis)
  - Gonadal tumor
  - Ovarian follicular cyst
  - Aromatase excess
  - HCG-secreting tumor
  - Primary hypothyroidism (Van Wyck-Grumbach)
  - Exogenous sex steroid exposure

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Differential Diagnosis of Precocious Puberty

- Incomplete pubertal development
  - Premature thelarche
  - Premature pubarche
  - Premature menarche

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Premature Thelarche

- Unilateral or bilateral breast development
- Minimal clinical features of estrogen exposure
- Normal growth with normal bone age
- 60% occurs between ages of 6-24 months (rare after 4 years)
- Most will have normal timing of menses
- 10% eventually develop true (central) precocious puberty

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Premature Thelarche

- In 863 Chinese girls ≤ 2 years of age, premature thelarche resolved in 89.3% before age 3. However, it persisted in 10.7 % and some progressed to central precocious puberty Wang YM et al 2013
- No studies have identified radiographic or hormonal profiles that accurately distinguish those who will progress from those who do not

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Incomplete Pubertal Development

- Premature adrenarche
  - May present with acne, pubic hair, body odor
  - Normal growth velocity and bone age
  - Increased incidence among CAH carriers and those with IUGR
  - Slightly advanced onset of true puberty
  - Increased (15-20%) risk of PCOS
- Premature menarche
  - May be due to follicular cyst
  - May not be true menses (shedding of endometrial lining)
  - May represent foreign body, trauma, sexual abuse, or tumors of the genital tract
  - Also consider other origins of bleeding (urethral, rectal)

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Central Precocious Puberty

- Early activation of the HPG axis
- Same physiology as normally-timed puberty
- Estimated incidence of 1:5,000-1:10,000
- Majority (~90%) of cases in girls are idiopathic
- ~50% of cases in boys are idiopathic
- Much more common in girls

Author	Year	Country	Ratio (male:female)
Thomsdrup [5]	1961	Denmark	1:4.1
UCSF [2]	1981	USA	1:1.2
Bridges *et al.* [6]	1994	UK	1:23.0
ISGPP [7, 8]	2000	Italy	1:9.5
Chemaitilly *et al.* [9]	2001	France	1:8.8
Ouriac-Klein *et al.* [10]	2001	USA	1:1.1

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Central Precocious Puberty

- International adoption
  - Primarily if immigrating to countries with improved socioeconomic conditions
  - Girls > boys
  - Not necessarily associated with nutrition, body weight, or body fat
  - Some may be due to birth date discrepancies

	Origin	No. of cases (2000–2009)	Σ population at risk (2000–2009)	RR (95% CI)
Sex				
Male	Born in Spain	17	17,486,913	
Male	Adopted	5	145,210	
Male	Immigrant	0	1,553,130	
Female	Born in Spain	155	14,447,403	
Female	Adopted	39	148,200	
Female	Immigrant	22	1,327,462	
Female				11.30 (7.47–18.04)
Adoption				25.62 (18.19–35.33)
Immigration				1.42 (0.88–2.16)

Central Precocious Puberty

- Intracranial tumor
  - Tumors may disrupt the neurons that are stimulatory or inhibitory to the control of the HPG axis
    - (astrocytoma, craniopharyngioma, ectopic pinealoma, ependymoma, optic glioma associated with NF1 or Tuberous Sclerosis, other glioma)
  - Secrete gonadotropins themselves
    - LH- secreting adenoma

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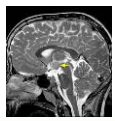
Central Precocious Puberty

- Congenital brain anomaly
  - Hypothalamic hamartoma- lesion consisting of hypothalamic tissues
    - Can secrete GnRH and is independent of the normal inhibitory mechanisms
    - Precocious puberty + gelastic seizures, behavioral issues, mental retardation
    - Boys > Girls
    - Can present as early as 2 years old



http://www.medscape.com/viewarticle/524_2-Hypothalamic_Hamartoma_Cases2007-3

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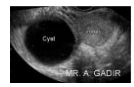
Peripheral Precocious Puberty

- Benign ovarian follicular cysts
  - Can transiently secrete estrogen
  - Can present with breast development, genital maturation, and sometimes, can result in vaginal bleeding
  - Can occur normally, due to Gn-dep. precocious puberty, or McCune Albright Syndrome
  - Usually self-limited



http://www.gynecologistsu.com/images/ovarianandcysts/ovarian_2PG.htl

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Diagnostic Evaluation

- Detailed history
  - Pubertal signs that are present
  - Timing of signs
  - Growth acceleration
  - Any exposures
  - Constitutional symptoms
  - Headaches, vision changes, abdominal pain
  - Exposures
- Family history → parental heights and timing of puberty

Girls: $\frac{(\text{Father's ht} - 13\text{ cm or } 5\text{in}) + \text{Mother's ht}}{2}$

Boys: $\frac{(\text{Mother's ht} + 13\text{ cm or } 5\text{ in.}) + \text{Father's ht}}{2}$

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Diagnostic Evaluation

- Think of the clinical findings
  - Breast development vs. pubic hair development vs. both
  - Enlarged testes
- LH and FSH
  - GnRH Stimulation test
- Estradiol or Testosterone

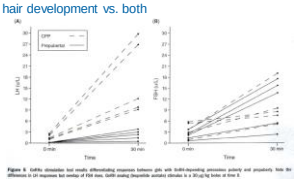

Figure 6 GnRHa stimulation test results differentiating responses between girls with GnRH-dependent precocious puberty and prepubertal. Note the differences in LH responses but overlap of FSH data. GnRH analog (leuprolide acetate) stimulus is a 30 μg/kg bolus at time 0.

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Diagnostic Evaluation

- DHEA-S, Androstenedione, 17-OH-Progesterone
  - if virilized, concerned for adrenal pathology
- TSH and free T4
  - If symptoms concerning for hypothyroidism
- Bone Age *
- MRI Brain
  - higher yield in younger children (<6) and boys

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Management

- Pediatricians can manage conditions such as premature thelarche and premature adrenarche
- However, because these conditions may represent early precocious puberty, close follow up is warranted
- Monitor every 3-6 months

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Management

- For patients with true precocious puberty or other Endocrine conditions that may cause pubertal development (CAH, McCune Albright, Testotoxicosis, etc.)
- Rapid progression of puberty
- Referral to Endocrinology is warranted

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Management

- Initial treatment should focus on treating any underlying causes
  - Surgery, chemotherapy, or radiation for intracranial tumors
  - Hydrocortisone for CAH
  - Thyroid replacement for hypothyroidism
  - Removal of exogenous steroid exposure

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Management

- Treatment for central precocious puberty can involve the use of GnRH analogs
  - Nafarelin (800 mcg BID) or Busrelin (20-40 mcg/kg)
    - Nasal spray given 3-4 times daily or daily subQ injections
    - Compliance is an issue
  - Leuprolide 0.3 mg/kg (7.5-15 mg)
    - A depot preparation which is given IM
    - Can be given qmonth or q3months
    - A study by Carel et al, 2002 demonstrated equal effectiveness with the 3 month preparation

http://www.mims.com/resources/diagnosis/images/2010/8004_DRP80006-JCC9-8803-B7D2-2C1C9F8A0877/suppository-100kg.jpg

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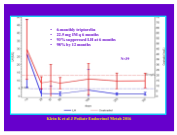
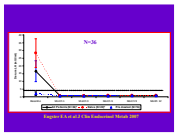


Klein K et al J Pediatr Endocrinol Metab 2016



Eugster E Carel J Clin Endocrinol Metab 2016

Treatment Options for CPP: Extended Release GnRHa Formulations

- 3-monthly GnRH analogs
  - used in Europe in children with CPP
  - a paucity of controlled, randomized studies
  - 3-monthly leuprolide approved in the US in 2011
- 6-monthly depot triptorelin
  - approved in the US in 2017
  - add'l 6-month preparations under investigation
- Histelin subcutaneous implant
  - approved in the US in 2007

Management

- Side effects:
  - Headaches
  - Hot flashes
  - Sterile abscesses (with subQ injections)
  - Decreased bone mineral density- normalizes after discontinuation
- Studies have demonstrated improvements in predicted adult height with treatment in children under 6, while children over 6 do not have significant height gain
- There is no evidence to support that treatment with GnRHa improves psychosocial outcomes

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How Should Treatment be Monitored?

- Auxologic parameters
  - growth velocity
  - Tanner staging
  - skeletal maturation
- Biochemical parameters
  - GnRH/GnRHa stimulation test
  - sex steroids
  - random US LH
    - pubertal value is not indicative of lack of suppression
  - kisspeptin?

Author	Year of publication	N	Years of GnRHa treatment	Adult height achieved (cm)	Increase above predicted (cm)
Heger	1999	50 girls	4.4 ± 2.1 years	160.6±8.0	5.7
Antoniazzi	2000	71 girls	16-56 months	154.4±5.6	2-7
Lazar	2007	115 girls	2.8-4.8 years	160.35±5.05	5
Pasquino	2008	87 girls	4.2 ± 1.6 years	159.8±5.3	5.1
Nabhan	2009	26 girls	3.6 ± 2.1 years	163±7.6	4.5
Magiakou	2010	33 girls	2.75 years	158.5	6.95
Poomvathorn	2011	47 girls	3.4 ± 1.5 years	158.6±5.2	4.7
Bertelloni	2015	25 girls	3.05 ± 0.9 years	158.25±5.8	3
Lee	2018	84 girls	2.98 ±.73 years	160.1±5	4

Eugster EA J Endocrinol Soc 2019

PREP 2018

- A girl aged 5 years 10 months is brought for evaluation of early puberty.
- Breast development started at about age 5 years, pubic hair was noted 2 months ago, and whitish vaginal discharge started in the past week.
- Physical findings show Tanner III breast development and Tanner II pubic hair development. Her vaginal mucosa appears pale.
- Her bone age study is interpreted as 10 years.
- Laboratory evaluation shows the following results:

Laboratory Test	Result
Third-generation LH	0.75 mIU/mL (0.75 IU/L)
FSH	0.45 mIU/mL (0.45 IU/L)
Estradiol	34 pg/mL (124.81 pmol/L)

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PREP 2018

- Cranial MRI shows a normal hypothalamus and pituitary gland, with normal ventricles and no focal lesion.

Of the following, the MOST likely outcome of treatment of this girl is :

A. Decrease in peak bone mass
B. Decrease in psychological distress
C. Gain in adult height of 5 cm
D. Risk of vaginal bleeding

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ANSWER is D

- The girl in the vignette has CPP. She has thelarche that started around age 5 years, which has progressed to Tanner stage III, and estrogenization of her vaginal mucosa. Her bone age is advanced because of exposure to sex steroids. Her third-generation LH of greater than 0.3 mIU/mL (> 0.3 IU/L).
- Not everyone who has CPP warrants GnRH agonist treatment, and the decision to treat is based on several factors. These include age at presentation, rate of pubertal progression, and predicted adult height.
- Therapy with a GnRH agonist is indicated for girls who have onset of CPP at younger ages (particularly before 6 years of age), have rapid progression of puberty, and an advanced bone age that predicts a compromised adult height below normal standards and genetic potential.

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ANSWER D

- Another effect of GnRH agonist therapy may be vaginal bleeding occurring within the first few weeks of starting treatment. This is because GnRH agonist treatment initially stimulates estradiol production before suppression of the HPG axis, resulting in estradiol withdrawal.
- For girls, if the onset of CPP is before 6 years of age (like the girl in the vignette), GnRH agonist treatment results in an average gain in adult height of 9 to 10 cm, compared with a gain of 4 to 7 cm if the onset occurs between 6 and 8 years of age. The rate of pubertal progression should also determine the need to treat; many girls (particularly with onset after 6 years of age) have puberty that is slowly progressive and do not require treatment. In general, boys with CPP occurring before 9 years of age should be treated
- Therapy with GnRH agonists appears safe in the long term. There do not seem to be long-term effects on the HPG axis or an increased risk of obesity. Although there may be a slight reduction in bone mineral density during treatment, this reduction is transient, and peak bone mass is preserved after treatment has been discontinued.

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Thank You

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