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No pubertal growth spurt, rapid bone maturation, and menarche post GnRHa treatment in girls with precocious puberty

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Authors

Briscoe, Audrey

Chen, Katherine

Klein, Karen O

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No Pubertal Growth Spurt, Rapid Bone Maturation, and Menarche Post GnRHa Treatment in Girls with Precocious Puberty

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Classification:	Puberty
Keywords:	precocious puberty, Leuprolide, menarche, GnRHa
Abstract:	<p>Objective To study total growth, rate of bone maturation and menarche after discontinuation of Gonadotropin releasing hormone agonist (GnRHa) treatment for central precocious puberty (CPP).</p> <p>Methods Twenty girls with CPP on treatment with GnRHa were followed from discontinuation of treatment to final height (FH). Height, height velocity (HV), and bone age were measured every 6 months. Age at menarche was collected.</p> <p>Results Once treatment is discontinued, rate of bone maturation (bone age [BA]/chronological [CA]) accelerated from 0.7 ± 0.3 at end of treatment to 1.2 ± 0.8 post treatment, similar to BA/CA prior to treatment. BA at treatment discontinuation ranged from 11 – 14 years. On average, treatment was stopped when CA was within 9 months of BA.</p> <p>All girls continued to grow from end of treatment to menarche averaging an increase of 4.7 ± 3.7 cm, with HV 3.2 ± 2.0 cm/y. Post-menarche they grew an additional 4.6 ± 2.1 cm, with HV 2.4 ± 1.9 cm/y. Acceleration of HV was not seen post treatment. The younger the BA at initiation or completion of treatment, the longer time to menarche. No one had menarche prior to a BA of 12.5 y.</p> <p>Conclusion A pubertal growth spurt does not usually occur after treatment with GnRHa in girls with CPP. Rate of bone maturation accelerates post treatment. These factors are important in assessing optimal height outcome and decisions regarding cessation of treatment. This study will help clinicians give patients and families better estimates of growth and onset of menarche post treatment.</p>

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SANTA BARBARA • SANTA CRUZ

PEDIATRIC ENDOCRINOLOGY DIVISION
DEPARTMENT OF PEDIATRICS, 0831
SCHOOL OF MEDICINE

9500 GILMAN DRIVE
LA JOLLA, CALIFORNIA 92093-0831
TEL: (619) 543-5238
FAX: (619) 543-3575

August 29, 2022

Thank you for your review of our manuscript entitled “No Pubertal Growth Spurt, Rapid Bone Maturation, and Variable Menarche Post GnRHa Treatment in girls with Central Precocious Puberty” for publication in *The Journal of Pediatric Endocrinology & Metabolism*.

We are submitting a revised version per the reviewers’ comments. A point by point rebuttal is as follows:

Reviewer: 1

“This is an outstanding manuscript reporting results from a study that validates what many in this field believed but had insufficient data to confirm. While the study is relatively small, it is extremely well designed, conducted and analyzed. This paper will provide the community with important information on the management of this population of patients. The only, very minor, suggestion I have is to go back and have the bone age films read by a single, blinded individual (if this was not already done). This will further strengthen the already excellent data presented in this manuscript.”

Authors’ response: The bone age readings were by a single, blinded individual. The methods contained the statement of the single individual, so we added the word, “blinded” which was how the readings were done. We also added that 2 investigators read the images, as AB completed her fellowship prior to end of the study. Page 5, line 111, now reads, “The bone maturation was assessed with a left hand radiograph (BA), interpreted by **one of two blinded investigators (AB, KK)** according to the Greulich and Pyle method (11). **There were no differences in readings between investigators on 20 independently read images.**”

Reviewer: 2

“1. It would be helpful if the authors included the number of girls in their clinic eligible for the study, the number who consented and the number who dropped out before completion. I was surprised that “Growth was considered complete when 3 consecutive heights were all within 0.5 cm ($HV \leq 0.5$ cm/yr)”. Wouldn't one measurement with such a low GV have sufficed to establish final height, and did they lose any patients because they dropped out before the 3rd visit showing no growth?”

Authors’ response: This is an excellent point. Three heights were used to be sure we captured end of height growth. Even though we are very careful with our stadiometer height measurements, we know that variability is possible and we wanted a study ensuring adult height data. Page 5, line 116, was edited as follows, “All girls participating in the study had a BA x-ray obtained every 6 months. Growth was considered complete when 3 consecutive heights were all within 0.5 cm ($HV \leq 0.5$ cm/yr), **to ensure no further growth from measurement error.**” We do not have record of number of girls to whom the study was offered, but we added the following sentence about those who dropped out on page 4, line 83, **“Twenty-one girls agreed to participate.**”

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3 One girl dropped out prior to end of growth. One girl did not return for confirmatory end of growth height
4 measure, but was included as last two height measures were within 0.7 cm and bone age was 15 years. We
5 suspect that follow up was so consistent because these girls were treated in our clinic by one provider for
6 many years and were thankful for continued care.”
7

8 “2. I would like to see a better discussion of the cost-implications of their findings. For many girls with CPP, the
9 main rationale for treatment is not to improve on PAH, which is often normal in the girls who are tall at the time of
10 diagnosis, but to mitigate the stress of early menses. I have tended to stop treatment around age 10 in such girls if I
11 feel they could handle menses by age 11. Continuing treatment until age 11-12.5, as was standard in this cohort,
12 should in my view, be considered mainly in those girls with a PAH which is subnormal (e.g. <155 cm), even if the
13 PAH is below the MPH when parents are tall. An extra year or 2 of GnRH therapy can cost quite a bit and may not
14 be needed routinely.”
15

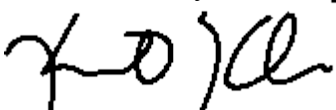
16 Authors' response: The cost-implications are not the focus of this study or discussion, so the editors can decide
17 whether to add the following to the discussion or not. Other than cost-implications, the reviewer's question raises the
18 discussion of whether longer treatment duration affects the results, so the following was added to page 12, line 259,
19 “The girls in this study were all treated until almost 11 yo or more in order to maximize height benefit as well as
20 have their physical findings of puberty coincide with their peers. When the primary goal of treatment is prevention
21 of early menarche, treatment is often discontinued between 10 – 11 yo, anticipating onset of menarche on average 18
22 months post treatment. While not the focus of this study, the cost-implications of continuing treatment should
23 always be kept in mind (reference added: Kaplowitz PB, Backeljauw PF, Allen DB. Toward more targeted and cost-
24 effective gonadotropin-releasing hormone analog treatment in girls with central precocious puberty. Horm Res
25 Paediatr 2018;90(1):1-7). Aside from cost-implications, however, the range of onset of menarche is 3 months to 2.5
26 years post treatment, similar to other published studies. Therefore, the older age at discontinuation in this cohort is
27 unlikely to have affected the results of time to menarche or growth post treatment. It is always clinically relevant to
28 inform families that a 10 yo girl who stops treatment may have menarche by 10 years 3 months, which would still be
29 quite early after years of treatment to delay menarche.”
30
31

32 “3. It would be nice if we could advise parents as to how long to menarche after cessation of therapy and yet this and
33 other studies show that the interval is between 3 and 20 months. Do the authors have any theories as to why this is
34 so variable?”
35

36 Authors' response: We continue to look for predictors of this variability, and add for the first time, some data on the
37 relationship with bone age. We added the following sentence to page 13, line 291, “Since time to menarche post
38 treatment is multifactorial and not yet able to be predicted, this study adds some guidelines and suggests
39 continuation of treatment beyond a bone age of 12.5 years in younger girls, where earlier menarche
40 continues to be a concern.”
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45 We thank you for your consideration of this manuscript and hope it is not acceptable for publication.

46 Yours sincerely,

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52 Karen O. Klein
53 Division of Pediatric Endocrinology
54 University of California San Diego
55 Rady Children's Hospital
56 kklein@ucsd.edu
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3 1 **8/529/22**
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6 2 **No Pubertal Growth Spurt, Rapid Bone Maturation, and Menarche Post GnRHa**
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8 3 **Treatment in Girls with Precocious Puberty**
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10 4
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12 5 **Running Title:**

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15 6 **Growth and Menses in CPP**
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19 8 Audrey Briscoe, Katherine Chen, Karen O. Klein
20

21 9 Division of Pediatric Endocrinology, Rady Children's Hospital San Diego, San Diego, and

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23
24 10 Department of Pediatrics, Division of Pediatric Endocrinology, University of California San

25
26 11 Diego, San Diego, CA 92103, USA
27

28
29 12 Corresponding author:

30
31 13 Karen O. Klein, MD

32 14 3020 Children's Way, MC 5103

33 15 San Diego, CA 92123

34 16 Tel: 858-966-4032

35 17 Fax: 858-966-6227

36
37 18 ORCID ID - **0000-0002-7953-4691**

38 19 e-mails: kklein@ucsd.edu; audrey.briscoe@kp.org; katherinechen97@gmail.com
39

40 21 Keywords: precocious puberty, Leuprolide, LH, growth, menses, menarche
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42

43 23 This work was supported by AbbVie, Inc. through an investigator initiated project. AbbVie did
44 24 not participate in the data analysis, writing or interpretation of data.
45 25

46 26 **Disclosure Summary**
47

48 27 Karen Klein is a consultant for AbbVie Pharm, Arbor Pharm, and Tolmar Pharm. Audrey

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51 28 Briscoe and Katherine Chen have nothing to disclose
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3 31 **Abstract**
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7
8 33 *Objective* To study total growth, rate of bone maturation and menarche after discontinuation of
9
10 34 Gonadotropin releasing hormone agonist (GnRHa) treatment for central precocious puberty
11
12 35 (CPP).
13

14 36 *Methods* Twenty girls with CPP on treatment with GnRHa were followed from discontinuation
15
16
17 37 of treatment to final height (FH). Height, height velocity (HV), and bone age were measured
18
19 38 every 6 months. Age at menarche was collected.
20

21 39 *Results* Once treatment is discontinued, rate of bone maturation (bone age [BA]/chronological
22
23 40 [CA]) accelerated from 0.7 ± 0.3 at end of treatment to 1.2 ± 0.8 post treatment, similar to
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25 41 BA/CA prior to treatment. BA at treatment discontinuation ranged from 11 – 14 years. On
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27 42 average, treatment was stopped when CA was within 9 months of BA.
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31 43 All girls continued to grow from end of treatment to menarche averaging an increase of 4.7 ± 3.7
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33 44 cm, with HV 3.2 ± 2.0 cm/y. Post-menarche they grew an additional 4.6 ± 2.1 cm, with HV $2.4 \pm$
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35 45 1.9 cm/y. Acceleration of HV was not seen post treatment. The younger the BA at initiation or
36
37 46 completion of treatment, the longer time to menarche. No one had menarche prior to a BA of
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39 47 12.5 y.
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42 48 *Conclusion* A pubertal growth spurt does not usually occur after treatment with GnRHa in girls
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44 49 with CPP. Rate of bone maturation accelerates post treatment. These factors are important in
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46 50 assessing optimal height outcome and decisions regarding cessation of treatment. This study will
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48 51 help clinicians give patients and families better estimates of growth and onset of menarche post
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50 52 treatment.
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54 **Introduction**

55 Gonadotropin releasing hormone agonist (GnRHa) treatment is standard of care for central
56 precocious puberty (CPP) (1-4). The treatment slows or halts pubertal progression, slows the rate
57 of bone maturation, suppresses gonadotropins, and usually decreases height velocity (HV) to
58 normal pre-pubertal levels. Predicted adult height (PAH) continues to improve while on
59 treatment, and then slowly decreases post treatment as rapid bone maturation resumes.

60 The decision regarding when to stop treatment needs to be individualized (5) and is based on
61 multiple factors. These include the child reaching an appropriate age for mid-puberty to resume
62 and a PAH reasonable for genetic potential, with caution that PAH may decrease once treatment
63 is discontinued (6). After discontinuation of GnRHa, the pubertal growth spurt typically does
64 not resume, however growth will continue at a slower velocity until cessation of growth. This
65 emphasizes the importance of not stopping treatment prematurely, as the remaining growth may
66 be minimal. There are limited studies of growth and HV after discontinuation of GnRHa,
67 especially as related to onset of menses (7). We studied rate of bone maturation and growth after
68 GnRHa treatment was stopped. We hypothesized that HV will not accelerate after treatment is
69 discontinued, and rate of bone maturation will accelerate. These results are helpful to parents
70 anticipating pubertal development, growth and menses post treatment, and provide important
71 information for the physician when deciding how long to continue GnRHa treatment based on
72 anticipated growth and menarche post treatment.

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77 **Materials and Methods**

78 *Study population*

79 All girls in our pediatric endocrinology clinic (Rady Children's Hospital, San Diego, CA) who
80 were treated with the GnRHa Lupron Depot Ped (8,9) for CPP were offered participation in this
81 study once ready to discontinue treatment. Recruitment took place between 2009 – 2012, and
82 study follow-up visits were completed by 2016 once all girls reached final height. Determination
83 of treatment cessation was based on physician judgement and parent request. Twenty-one girls
84 agreed to participate. One girl dropped out prior to end of growth. One girl did not return for
85 confirmatory end of growth height measure, but was included as last two height measures were
86 within 0.7 cm and bone age was 15 years. We suspect that follow up was so consistent because
87 these girls were treated in our clinic by one provider for many years and were thankful for
88 continued care. All girls and their parents signed an assent and consent approved by our
89 institutional review board. All authors complied with the World Medical Association Declaration
90 of Helsinki regarding ethical conduct of research involving human subjects.

91 Girls were included if chronological age (CA) at onset of pubertal symptoms was less than 8
92 years old, breast development was consistent with at least pubertal stage 2 at diagnosis, bone age
93 (BA) was more than 2 SD above the mean for CA or PAH was at least 2 inches (5.08 cm) below
94 midparental height (MPH). Pubertal stage was defined according to a modification of Tanner's
95 description (10) to include breast palpation. Two patients were included without definitive data
96 on onset of breast development. Patient #8 is included even though age at onset of CPP is listed
97 at 8 y 4 m. This was by parent report of noticing breasts, however, since no physician saw her
98 prior to that time and breast stage was already fully stage 3 with BA 3 years advanced, we
99 suspect pubertal onset was likely prior to age 8 years. Patient #1 presented with menarche at 8 y

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3 100 10 m, She had stage 4 breast and a report that breast had been present since birth. Her BA was 3
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5 101 years advanced, so likely onset of CPP was less than 8 years old.

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8 102 CPP was defined as a peak LH level above 5 IU/L during an aqueous leuprolide stimulation test.

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10 103 All girls had idiopathic central precocious puberty. Girls were excluded if they had any other
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12 104 condition interfering with growth, such as skeletal dysplasia, cerebral palsy, or a chronic illness
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14 105 requiring treatment that may have impacted their growth potential. Stable patients with
15
16 106 intermittent asthma or patients on topical acne medication were included.
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21 108 *Study design*

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23 109 Girls underwent a general clinical examination and pubertal staging every 6 months until final
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25 110 height (FH) was reached. At each visit, height (using a Holtain stadiometer) and weight were
26
27 111 recorded. The bone maturation was assessed with a left hand radiograph (BA), interpreted by one
28
29 112 of two a single-blinded investigators (AB, KK) according to the Greulich and Pyle method (11).
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31 113 There were no differences in readings between investigators on 20 independently read images.
32
33 114 PAH was calculated at each visit according to Bailey-Pineau tables (11). All girls participating in
34
35 115 the study had a BA x-ray obtained every 6 months. Growth was considered complete when 3
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37 116 consecutive heights were all within 0.5 cm ($HV \leq 0.5$ cm/yr), to ensure no further growth from
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39 117 measurement error. Girls were asked to record all menstrual cycles in detail in a calendar, with
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41 118 duration, severity, and timing noted.
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49 120 *Statistical analysis*

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51 121 All data is presented as mean \pm SD. Linear regression analysis was used for correlations. MPH
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53 122 was calculated with parental report of height at the first visit; MPH=[maternal height
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3 123 (cm)+paternal height(cm)-13]/2. MPH was available for 19/20 subjects. Height velocity was
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5 124 calculated based on the data as cm per year change (cm/y).
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8 125 Rate of change of BA was calculated as the change in BA in years divided by time interval to
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10 126 yield a change in units of year per chronological year (y/y).
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19 130 **Results**

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21 131 Twenty girls remained in the study until FH was reached. Baseline characteristics are shown in
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23
24 132 Table 1, 2 and 3. GnRHa treatment was stopped at an average age of 11.8 ± 0.6 years (range
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26 133 $10.6 - 13.2$ years). Girls were treated for an average duration of 4.5 ± 2.4 years (range $1.5-10.4$
27
28 134 years). The average reported age at onset of puberty was 5.8 ± 2.1 years (range $1.0 - 8.4$ years).
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31 135 One girl was included in the study who had her onset of puberty estimated by parents at 8.4
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33 136 years, however she had rapid progression of puberty, her BA was 2 years advanced, and her
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35 137 PAH was below her MPH.
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40 139 *Bone maturation*

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42 140 BA at discontinuation of treatment ranged from 11 – 14 years (average 12.5 ± 0.8 years). The
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45 141 BA at the onset and end of treatment both had a negative correlation with time to menarche post
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47 142 treatment ($p < 0.01$). Girls with a younger BA at onset or end of treatment developed menarche
48
49 143 later than girls with an older BA at either time point during treatment ($p < 0.01$)(Figure 1). BA at
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51 144 end of treatment also had a negative correlation with the amount of growth accrued post
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3 145 treatment, such that the younger the BA at end of treatment, the greater overall growth post-
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5 146 treatment ($p < 0.01$) (Figure 2). No one had menarche prior to a bone age of 12.5 y.

7 147 The rate of change of BA advancement averaged 1.3 ± 0.15 prior to treatment, and decreased
8
9 148 during treatment to 0.7 ± 0.3 years per chronological year (y/y). Post treatment, rate of BA
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11 149 change accelerated to 1.2 ± 0.8 y/y (range 0 – 3.0y/y). (Table 2, Figure 3).

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14 150 On average, treatment was stopped when CA was within 9 months of BA. Three girls had a BA
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16 151 > 2 year beyond CA at end of treatment. They also had the 3 oldest BA at the end of treatment,
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18 152 but 2 girls surpassed their MPH (1 did not have MPH available).

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23 154 *Growth*

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25 155 Average HV on treatment was 4.8 ± 1.2 cm/y (range 2.9 - 7.6). All girls continued to grow from end
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27 156 of treatment to menarche with an average of 4.7 ± 3.7 cm, with an average height velocity of $3.2 \pm$
28
29 157 2.0 cm/y. On average, they grew an additional 4.6 ± 2.1 cm from menarche until FH, with a HV
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31 158 of 2.4 ± 1.9 cm/y during that time. (Fig 4) Only 2/20 girls, had an increased height velocity (>6
32
33 159 cm/yr) after treatment was discontinued, similar to a pubertal height velocity. Growth after
34
35 160 discontinuation of treatment ranged from 4.6 – 12.4 cm in girls who stopped GnRHa with a $BA \geq$
36
37 161 13 years, and 7.9 – 16.7 cm in girls who stopped GnRHa with a $BA < 13$ years.

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43 163 *Menarche*

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45 164 After treatment was discontinued, the average age at menarche was 13.2 ± 0.9 years, however
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47 165 ranged from 11.3 – 14.6 years. The average time from end of treatment to menarche was $15.2 \pm$
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49 166 7.4 months, with a range of 3 – 30 months. The younger the BA was at initiation or completion
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53 167 of treatment, predicted a longer time to menarche. Menses occurred at regular intervals (defined

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3 168 as cycles 21 – 35 days long) in some girls immediately post treatment, although other girls
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5 169 continued to have irregular menses up to 3 years post treatment. No predictions of time to
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8 170 regular menstrual cycles were found. When data was analyzed to compare girls with onset of
9
10 171 $CPP \leq 6$ yo compared to those > 6 yo, the only significant difference, other than the obvious age
11
12 172 and BA, was age at onset of menarche. The younger girls had menarche on average one year
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14 173 later than the older girls, but at a similar BA.
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19 175 *Adult final height*

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21 176 FH occurred an average of 2 years post menarche, with a range of 0 to 3.7 years. FH was within
22
23 177 3 inches of MPH in 18/19 (1 child without MPH data) girls. Average difference between MPH
24
25 178 and FH (MPH-FH) was 0.5 ± 6.0 cm. MPH was reached or surpassed by 11/19 (58%) girls
26
27 179 treated with GnRHa for CPP. One girl attained a FH 14 cm below MPH, however her parents
28
29 180 were tall (MPH =170 cm), pubertal onset was quite early at 5.5 years and her BA was 3.75 years
30
31 181 advanced at start of treatment. Another girl attained a FH quite below her MPH, however she
32
33 182 also had 2 tall parents (MPH = 176.5 cm) and onset of puberty at age 1.5 years old, although was
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35 183 able to reach a FH of 168 cm (Table 3).
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42 185 **Discussion**

43
44 186 Time to menarche is a great concern for many children and their families. The range of onset of
45
46 187 menarche post GnRHa treatment is consistent across studies (12-15) from 3 months to 3 years.
47
48 188 The present study confirms that range but shows for the first time the relationship between BA
49
50 189 and menarche. We found that the younger the BA was prior to treatment or the younger the BA
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52 190 was at the end of treatment, predicted a longer time to menarche. No girls had menarche prior to
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3 191 BA of 12.5 years. When girls were compared by onset of CPP ≤ 6 years versus > 6 yo, the
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5 192 younger girls had menarche on average one year later than the older girls, but at a similar BA.
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7 193 This supports the importance of BA in predicting menarche. There were no other differences
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9
10 194 between these 2 groups, supporting the robustness of this population with truly rapidly
11
12 195 progressing CPP, rather than a mixed population of early normal puberty and CPP. This is one
13
14 196 of the strengths of the population, since many publications likely include some early normal
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16 197 puberty when girls close to 8 years old are studied.
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19 198
20
21 199 Rate of BA advancement prior to treatment in girls with CPP is accelerated. On GnRHa
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23 200 treatment, rate of advancement slows to less than 1 year per year when treatment is optimal, and
24
25 201 therefore leads to increases in growth potential and FH (20). Once treatment is stopped, we
26
27 202 suspected that rate of BA advancement accelerates, and this is the first study with data to support
28
29 203 that pathophysiology. Prior to GnRHa treatment rate of BA advancement in this population on
30
31 204 average was 1.3 years per chronological year (5). This decreases to an average of 0.7 years per
32
33 205 year on treatment. Post treatment, rate of BA advancement accelerates back to pretreatment rapid
34
35 206 maturation averaging 1.2 years per year. This is expected since whatever process causes rapid
36
37 207 bone maturation in CPP, is not cured by GnRHa treatment, but rather slowed down during
38
39 208 treatment. Lazar et al (21) reported data from 115 girls post-GnRHa treatment. They describe
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41 209 greater height gain post treatment in girls who had onset of puberty prior to 6 years old compared
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43 210 to older girls. Final height in the older groups was less than PAH at end of treatment. They
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45 211 measured BA every 12 months and report that BA at end of treatment significantly contributed to
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47 212 prediction of height gain post treatment. However, they do not report change in BA post
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49 213 treatment. They raised the question of whether post-treatment growth would have been greater if
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3 214 BA was closer to 11 at end of treatment. The present data support the opposite hypothesis, since
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5 215 rate of BA advance accelerates post treatment, stopping treatment at an older BA may lead to
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8 216 greater final height, achieved by more growth on treatment rather than more growth post-
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10 217 treatment. Shim et al also looked at growth post-GnRHa treatment in 85 boys but compared only
11
12 218 PAH at end of treatment to final height, and did not delineate BA or growth rate changes over
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14
15 219 the years post treatment (22).

16
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19 221 On average, treatment was stopped when CA was close to BA. Adequate pubertal suppression
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21 222 with GnRHa theoretically corrects the discrepancy between BA and CA seen prior to treatment.
22
23 223 The girls in this study who did not reach a CA within 2 years of BA prior to end of treatment,
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25 224 were treated until an older BA than the rest of the girls, which was likely necessary to achieve
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27
28 225 improved FH outcomes. This supports the likely the importance of duration of treatment for
29
30 226 optimal height outcome. Of course, we cannot know what height the girls would have achieved
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32
33 227 if treatment had been discontinued earlier, but we have shown the rapid acceleration of rate of
34
35 228 bone maturation post treatment so it would be unlikely they would have reached the same FH.
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37
38 229 Previous studies showed that earlier onset of treatment, less BA advancement, and less delay
39
40 230 from onset of CPP to onset of treatment have taller height outcomes as compared to MPH (6,16-
41
42 231 19). In the present study, girls with less BA advancement had greater growth post treatment.
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44
45 232 This is the first study to quantify growth and growth rate between end of treatment and menarche
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47 233 and between menarche and FH. This is very important for clinicians and families when making
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49 234 decisions about the timing for cessation of GnRHa treatment. Those decisions cannot be based
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51 235 on expectations for resumption of a pubertal growth spurt post treatment. Only 2 girls in this
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54 236 population had increased HV to > 6 cm/y post treatment. All others grew at ≤ 5 cm/y after

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3 237 GnRHa was stopped. An interrupted pubertal growth spurt does not resume post GnRHa
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5 238 treatment for CPP.
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10 240 The lack of rapid pubertal growth post treatment is likely related to growth plate senescence. Our
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12 241 understanding of growth plate senescence includes the effect of estrogen to first stimulate growth
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14 242 plate chondrogenesis and therefore linear growth, while simultaneously decreasing the number of
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16 243 resting zone chondrocytes, accelerating the rate of chondrocyte proliferation leading to earlier
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18 244 proliferative exhaustion with eventual growth plate fusion (23,24). The early exposure of
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20 245 estrogen in precocious puberty causes early growth plate senescence. Perhaps GnRHa treatment
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22 246 is usually timed to interrupt this process at the point when estrogen has already diminished
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24 247 enough chondrocytes, such that as bone aging continues during treatment and no further increase
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26 248 is possible post treatment. The older the BA was at the beginning of treatment, the less growth is
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28 249 accrued post treatment. We can interrupt the process of CPP causing rapid maturation of BA, but
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30 250 the process of senescence, although slowed during treatment, is not stopped, so we cannot regain
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32 251 all the growth potential that was lost. This is further support of continuation of GnRHa longer in
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34 252 those girls with late onset of treatment who have short height potential compared to MPH.
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36 253 It cannot be determined from this study whether growth would have been different if treatment
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38 254 was stopped earlier in the girls with more advanced BA. However, in all girls HV was good
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40 255 throughout treatment, there was similar amount of growth post treatment, and height outcomes
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42 256 compared to MPH were similar across all girls. This suggests that the individual treatment
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44 257 decisions of when to stop GnRHa treatment led to the best expected outcomes.
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51 258 The girls in this study were all treated until almost 11 yo or more in order to maximize height
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54 259 benefit as well as have their physical findings of puberty coincide with their peers. When the
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3 260 primary goal of treatment is prevention of early menarche, treatment is often discontinued
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5 261 between 10 – 11 yo, anticipating onset of menarche on average 18 months post treatment. While
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7 262 not the focus of this study, the cost-implications of continuing treatment should always be kept in
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9 263 mind (25). Aside from cost-implications, however, the range of onset of menarche is 3 months to
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11 264 2.5 years post treatment, similar to other published studies. Therefore, the older age at
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13 265 discontinuation in this cohort is unlikely to have affected the results of time to menarche or
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15 266 growth post treatment. It is always clinically relevant to inform families that a 10 yo girl who
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17 267 stops treatment may have menarche by 10 years 3 months, which would still be quite early after
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19 268 years of treatment to delay menarche.”
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24 269 The major strengths of this study include following girls to FH with measures of growth, bone
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26 270 maturation and menses every 6 months for as long as 5 – 6 years post GnRHa treatment. This
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28 271 study also has girls who continued GnRHa until 13 – 14 years with good growth during the
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30 272 treatment interval, as well as post treatment. We found that 18/19 had FH within 3 inches of
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32 273 MPH, with more than half of the girls reaching or surpassing MPH. The wide range of age at
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34 274 onset of puberty allowed assessment of age as a factor contributing to timing of menarche.
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40 276 The major limitations include the small number of participants, although this does show a real-
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42 277 world example from one center. All girls were offered participation, but not all girls wanted to
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44 278 continue to be followed every 6 months once treatment was discontinued, so there may have
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46 279 been some bias in those who continued coming. For example, those who did not continue follow
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48 280 up may have been obviously growing less and therefore not interested in continued bone age to
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50 281 assess potential growth. It is unlikely that those who preferred not to continue were those
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52 282 growing more rapidly, but that cannot be determined. Another limitation is that bone age at
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3 283 cessation of treatment was not randomized, so physician decisions to stop treatment could bias
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5 284 outcomes. However, it would not be ethical to randomize treatment cessation if physician
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8 285 assessment indicated possible benefit to continued treatment.
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12 287 In conclusion, the present study quantitates growth after treatment with GnRHa in girls with
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14 288 CPP. In most girls, there is no resumption of pubertal growth spurt post GnRHa treatment. Time
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17 289 to onset of menarche post-GnRHa treatment is proportionate to BA at the start as well as the end
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19 290 of treatment, with no girls in the present study having menarche prior to BA of 12.5 years. Since
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21 291 time to menarche post treatment is multifactorial and not yet able to be predicted, this study adds
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23 292 some guidelines and suggests continuation of treatment beyond a bone age of 12.5 years in
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25 293 younger girls, where earlier menarche continues to be a concern.
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28 294 Rate of bone maturation accelerates post treatment. These factors are important in assessing
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30 295 potential height outcome and the decision regarding timing for cessation of treatment. This study
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32 296 will help clinicians give patients and families better estimates of growth and onset of menarche
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34 297 post treatment.
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51 304 **References**

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53
54 305 1. Eugster EA. Precocious Puberty. J Clin Endocrinol Metab 2006; - 91(9); 15A-16A
55
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59
60

- 1
2
3 306 2. Pace JN, Miller JL, Rose LI. GnRH agonists: gonadorelin, leuprolide and nafarelin. Am Fam
4
5 307 Physician. 1991; Nov; 44(5):1777-82.
6
7
8 308 3. Kaplan SL, Grumbach MM. Clinical Review 14: Pathophysiology and treatment of sexual
9
10 309 precocity. J Clin Endocrinol Metab 1990; 71:785–789
11
12 310 4. Conn PM, Crowley WF. Gonadotropin-releasing hormone and its analogs. Annu Rev Med
13
14 311 1994; 45:391–405
15
16
17 312 5. Vargas Trujillo M, Dragnic S, Aldridge P, Klein KO. Importance of individualizing treatment
18
19 313 decisions in girls with central precocious puberty when initiating treatment after age 7 years or
20
21 314 continuing beyond a chronological age of 10 years or a bone age of 12 years. J Pediatr
22
23 315 Endocrinol Metab. 2021 Apr 15;34(6):733-739.
24
25
26 316 6. Klein KO, Barnes KM, Jones JV, Feuillan PP, Cutler, GB. Increased Adult Height in
27
28 317 Precocious Puberty after Long-Term Treatment with LHRH Agonists: The National Institutes of
29
30 318 Health Experience J Clin Endocrinol MetabEM 2001; 86: 4711 – 4716
31
32
33 319 7. Carel JC, Roger M, Ispas S, Tondu F, Lahlou N, Blumberg J, et al. Final height after long-
34
35 320 term treatment with triptorelin slow release for central precocious puberty: importance of statural
36
37 321 growth after interruption of treatment. French study group of Decapeptyl in Precocious Puberty.
38
39 322 J Clin Endocrinol Metab 1999;84:1973-8.
40
41
42 323 8. Wilson AC, Meethal SV, Atwood CS. Leuprolide acetate: a drug of diverse clinical
43
44 324 applications Expert Opin Investig Drugs. 2007 Nov; 16(11):1851-63.
45
46
47 325 9. Kappy MS, Stuart TE, Perelman AH, Clemons RD. Suppression of gonadotropin acetate by a
48
49 326 long-acting gonadotropin-releasing hormone analog (leuprolide acetate, Lupron depot) in
50
51 327 children with precocious puberty. J Clin Endocrinol Metab 1989; 69:1087–1089
52
53
54 328 10. Tanner JM. Growth at adolescence. 1966; 2nd ed. New York, NY: Appleton-Century-Crofts
55
56
57
58
59
60

- 1
2
3 329 11.. Greulich WW, Pyle SI. 1959 Radiographic Atlas of Skeletal development of the hand and
4
5 330 Wrist, 2nd Ed. Stanford, CA: Stanford University Press
6
7
8 331 12. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Group E-LGACC, et al.
9
10 332 Consensus statement on the use of gonadotropin-releasing hormone analogs in children.
11
12 333 *Pediatrics* 2009;123:e752-62.
13
14
15 334 13. Guaraldi F, Beccuti G, Gori D, Ghizzoni L. Management of endocrine disease: long-term
16
17 335 outcomes of the treatment of central precocious puberty. *Eur J Endocrinol* 2016;174:R79-87.
18
19 336 14. Poomthavorn P, Suphasit R, Mahachoklertwattana P. Adult height, body mass index and time
20
21 337 of menarche of girls with idiopathic central precocious puberty after gonadotropin-releasing
22
23 338 hormone analogue treatment. *Gynecol Endocrinol* 2011;27:524-8.
24
25
26 339 15. Neely EK, Lee PA, Bloch CA, Larsen L, Yang D, Mattia-Goldberg C, et al. Leuprolide
27
28 340 acetate 1-month depot for central precocious puberty: hormonal suppression and recovery. *Int J*
29
30 341 *Pediatr Endocrinol* 2010;2010:398639.
31
32
33 342 16. Mul D, Oostdijk W, Otten BJ, Rouwe C, Jansen M, Delemarre-van de Waal HA, et al. Final
34
35 343 height after gonadotrophin releasing hormone agonist treatment for central precocious puberty:
36
37 344 the Dutch experience. *J Pediatr Endocrinol Metab* 2000;13 Suppl 1:765-72.
38
39
40 345 17. Partsch CJ, Heger S, Sippell WG. Treatment of central precocious puberty: lessons from a 15
41
42 346 years prospective trial. German Decapeptyl Study Group. *J Pediatr Endocrinol Metab* 2000;13
43
44 347 Suppl 1:747-58.
45
46
47 348 18. Styne DM, Harris DA, Egli CA, et al. Treatment of true precocious puberty with a
48
49 349 potent luteinizing hormone-releasing factor agonist: effect on growth, sexual maturation, pelvic
50
51 350 sonography, and the hypothalamic-pituitary-gonadal axis. *J Clin Endocrinol Metab*. 1985;
52
53 351 61:142–151
54
55
56
57
58
59
60

- 1
2
3 352 19. Brito VN, Latronico AC, Cukier P, Teles MG, Silveira LF, Arnhold IJ, Mendonca BB.
4
5 353 Factors determining normal adult height in girls with gonadotropin-dependent precocious
6
7
8 354 Lazar L, Kuali R, Pertzalan A, Phillip M. Gonadotropin-suppressive therapy in girls with early
9
10 355 and fast puberty affects the pace of puberty but not total pubertal growth or final height. 2002;
11
12 356 87(5):2090-2094.
- 14 357 21. Lazar L, Padoa A, Phillip M. Growth pattern and final height after cessation of gonadotropin-
15
16 358 suppressive therapy in girls with central sexual precocity. 2007; 92(9):3483-3489.
- 18 359 22. Shim YS, Lim KI, Lee HS, Hwang JS. Long-term outcomes after gonadotropin-releasing
20
21 360 hormone agonist treatment in boys with central precocious puberty. 2020;PLoS ONE
22
23 361 15(12):e0243212
24
25 362 puberty treated with depot gonadotropin-releasing hormone analogs. J Clin Endocrinol Metab.
26
27 363 2008; Jul;93(7):2662-9
- 29 364 23. Lui JC, Nilsson O, Baron J. Recent research on the growth plate: Recent insights into the
30
31 365 regulation of the growth plate. *Journal of molecular endocrinology*. 2014;53(1):T1–9. Epub
32
33 366 2014/04/18. 10.1530/JME-14-0022
- 35 367 24. Weise M, De-Levi S, Barnes KM, Gafni RI, Abad V, and Baron J. Effects of estrogen on
36
37 368 growth plate senescence and epiphyseal fusion. Proc Natl Acad Sci U S A. 2001 Jun 5; 98(12):
38
39 369 6871–6876.
- 41 370 [25. Kaplowitz PB, Backeljauw PF, Allen DB. Toward more targeted and cost-effective](#)
42
43 371 [gonadotropin-releasing hormone analog treatment in girls with central precocious puberty. *Horm*](#)
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45 372 [Res Paediatr 2018;90\(1\):1-7](#)
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54 374 Table 1. Patient age and time to menarche
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<u>Patient ID</u>	<u>Ethnicity</u>	<u>CA at onset CPP</u>	<u>CA at start Rx</u>	<u>CA at stop Rx</u>	<u>Duration of Rx (y)</u>	<u>CA at Menarche</u>	<u>Time post Rx to Menarche (months)</u>	<u>Time menarche to FH (y)</u>
20	White	1.5	1.5	11.2	9.7	13.5	28.0	0.7
9	Hispanic	5.0	8.8	12.8	4.0	13.6	11.0	1.2
18	Hispanic	7.5	8.0	11.0	3.0	13.5	30.0	0.0
6	White	7.5	7.5	11.3	3.8	12.3	12.0	2.2
12	White	5.6	6.6	11.6	5.0	13.3	22.0	3.2
19	Asian	6.6	7.8	11.8	4.0	13.2	16.4	1.6
21	Hispanic	1.0	1.6	12.0	10.4	14.2	26.4	1.1
5	White	7.0	8.2	12.1	3.9	13.8	20.0	3.2
15	White	5.9	7.3	13.3	6.0	14.6	16.2	1.7
3	White	7.8	9.3	11.8	2.5	12.6	10.0	3.7
10	White	2.4	3.8	12.5	8.7	14.2	19.0	2.8
4	White	6.0	8.9	11.5	2.6	13.9	5.0	2.3
16	White	5.5	6.3	11.7	5.4	13.0	16.0	0.0
2	White	7.3	8.5	11.9	3.4	12.3	8.0	2.6
7	Hispanic	7.0	7.8	12.0	4.2	13.2	14.0	2.3
11	Hispanic	6.0	8.5	12.6	4.1	13.6	11.0	2.0
17	Hispanic	5.0	8.6	12.6	4.0	13.8	13.8	2.5
1	Hispanic	*	9.2	10.7	1.5	11.3	7.0	2.7
13	White	7.4	8.8	11.3	2.6	11.6	3.0	1.2
8	Asian	8.4	9.3	11.5	2.2	12.8	16.0	2.2
Average		5.8	7.3	11.8	4.5	13.2	15.2	2.0
Minimum		1.0	1.5	10.7	1.5	11.3	3.0	0.0
Maximum		8.4	9.3	13.3	10.4	14.6	30.0	3.7
SD		2.1	2.3	0.6	2.4	0.9	7.4	1.0

* menarche at 8.8, but breast onset not known
 BA = bone age, Rx = treatment, FH = final height, CA -
 chronological age, CPP = central precocious puberty

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379 Table 2. Bone age data during and after treatment with GnRH α

<u>Patient ID</u>	<u>BA start Rx (y)</u>	<u>BA/CA start Rx</u>	<u>BA end of Rx (y)</u>	<u>BA at menarche (y)</u>	<u>BA at FH (y)</u>	<u>BA/CA during Rx</u>	<u>BA/CA end Rx to menarche</u>	<u>BA/CA menarche to FH</u>
20	**	**	11.0	15.0	15.0	**	1.7	0.0
9	8.8	1.0	11.5	13.5	16.0	0.7	2.2	2.2
18	10.0	1.3	12.0	16.5	16.8	0.7	1.8	0.5
6	**	**	12.0	15.0	15.0	**	3.0	0.0
12	6.8	1.0	12.0	12.5	16.5	1.0	0.3	1.3
19	7.8	1.0	12.0	13.8	15.5	1.1	1.3	1.1
21	2.0	1.3	12.0	15.0	15.5	1.0	1.4	0.4
5	***	***	12.0	13.5	17.0	***	0.9	1.1
15	10.0	1.4	12.0	14.0	16.3	0.3	1.5	1.4
3	11.0	1.2	12.5	13.8	***	0.6	1.5	***
10	4.6	1.2	12.5	14.0	16.5	0.9	0.9	0.9
4	12.0	1.3	13.0	16.0	17.0	0.4	1.23	0.4
16	10.0	1.6	13.0	***	***	0.6	***	***
2	11.0	1.3	13.0	13.0	16.0	0.6	0.0	1.2
7	11.0	1.4	13.0	14.3	15.0	0.5	1.1	0.3
11	11.0	1.3	13.0	15.0	15.5	0.5	2.2	0.3
17	10.0	1.2	13.0	13.0	15.8	0.8	0.0	1.1
1	11.5	1.3	13.5	13.5	16.0	1.4	0.0	0.9
13	12.0	1.4	13.6	13.8	17.0	0.6	0.8	2.6
8	11.5	1.2	14.0	15.0	17.0	1.1	0.8	0.9
Average	9.5	1.3	12.5	14.2	16.1	0.7	1.2	0.9
Minimum	2.0	1.0	11.0	12.5	15.0	0.3	0.0	0.0
Maximum	12.0	1.6	14.0	16.5	17.0	1.4	3.0	2.6
SD	2.8	0.2	0.8	1.0	0.7	0.3	0.81	0.7

** came to us on treatment without records

*** missing data

BA = bone age, Rx = treatment, FH = final height, CA - chronological age

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383 Table 3. Growth changes during and after treatment with GnRH α

<u>Patient ID</u>	<u>Ht start of Rx (cm)</u>	<u>Ht end Rx (cm)</u>	<u>Growth end Rx to menarche (cm total)</u>	<u>HV end Rx to menarche (cm/y)</u>	<u>Ht at menarche (cm)</u>	<u>FH (cm)</u>	<u>CA at FH (y)</u>	<u>Growth menses to FH (cm total)</u>	<u>HV menarche to FH (cm/y)</u>	<u>MPH (cm)</u>	<u>MPH - FH (cm)</u>
20	**	154.9	7.4	3.2	162.3	168.0	14.2	5.7	8.5	176.4	8.4
9	134.0	152.7	2.6	2.8	155.3	161.0	14.8	5.7	5.0	156.1	-4.9
18	141.7	162.5	8.0	3.2	170.5	170.5	14.0	0.0	0.0	168.5	-2.0
6	**	155.6	2.6	2.6	158.2	165.2	14.5	7.0	3.2	157.3	-7.9
12	114.5	140.3	10.6	5.8	150.9	155.5	16.4	4.6	1.5	155.1	-0.4
19	122.8	152.7	10.3	7.5	163.0	164.7	14.8	1.7	1.0	161.1	-3.6
21	80.5	152.7	9.3	4.2	162.0	165.5	15.3	3.5	3.1	171.3	5.8
5	125.0	141.4	7.9	4.7	149.3	153.3	17.0	4.0	1.3	161.1	7.8
15	119.7	146.6	5.5	4.1	152.1	154.5	16.3	2.4	1.5	162.4	7.9
3	147.5	163.4	3.2	3.8	166.6	172.0	16.3	5.4	1.4	171.3	-0.7
10	106.5	160.0	10.5	6.6	170.5	176.7	17.0	6.2	2.2	168.8	-7.9
4	142.3	153.5	0.0	0.0	153.5	160.5	16.2	7.0	3.1	152.3	-8.3
16	120.7	147.6	3.0	1.3	150.6	155.7	15.8	5.1	0.0	170.0	14.3
2	136.9	162.9	2.1	3.1	165.0	169.5	14.9	4.5	1.7	165.0	-4.6
7	130.5	142.7	3.6	3.1	146.3	148.5	15.5	2.2	1.0	156.1	7.6
11	127.4	148.7	0.6	0.7	149.3	153.3	15.6	4.0	2.0	158.6	5.3
17	124.3	140.2	3.6	3.1	143.8	152.6	16.3	8.8	3.5	153.5	0.9
1	135.0	142.3	1.8	3.1	144.1	151.0	13.9	6.9	2.6	***	***
13	140.8	151.7	0.0	0.0	151.7	156.3	12.8	4.6	3.7	152.9	-3.4
8	147.5	155.8	1.4	1.0	157.2	160.4	15.0	3.2	1.5	156.1	-4.3
Average	127.6	151.4	4.7	3.2	156.1	160.7	15.3	4.6	2.4	161.8	0.5
Minimum	80.5	140.2	0.0	0.0	143.8	148.5	12.8	0.0	0.0	152.3	-8.3
Maximum	147.5	163.4	10.6	7.5	170.5	176.7	17.0	8.8	8.5	176.4	14.3
SD	16.4	7.6	3.7	2.0	8.3	7.9	1.1	2.1	1.9	7.4	6.7

** came to us on treatment without records

*** missing data

HV = height velocity, Rx = treatment, FH = final height, CA - chronological age, Ht – height, MPH = mid-parental height

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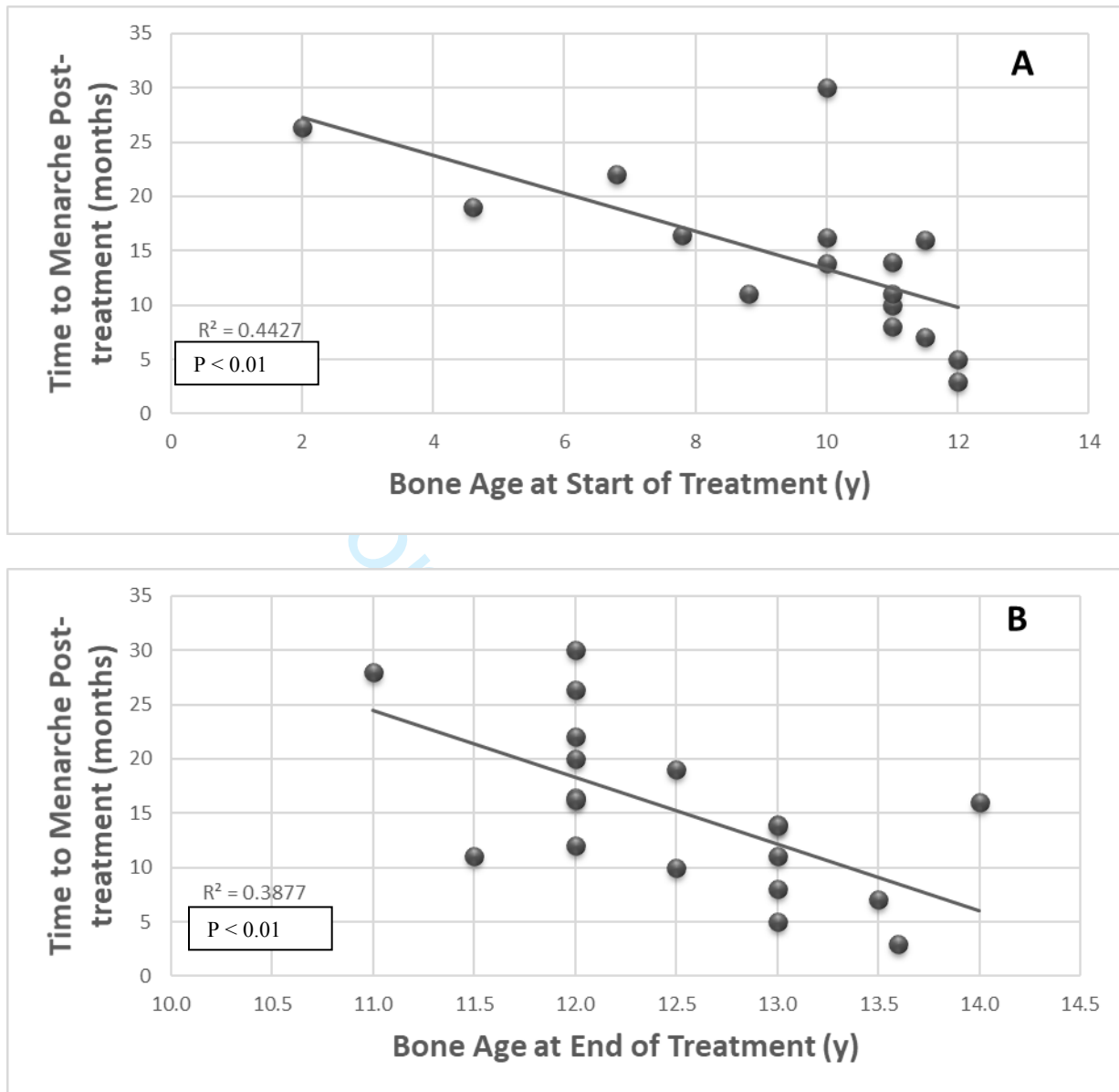
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387 **Figure Legends**

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3 388 Figure 1: Time to Menarche post GnRHa treatment by bone age at start of treatment (A) and by
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5 389 bone age at end of treatment (B)
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8 390 Figure 2. Total Growth post GnRHa treatment by BA at end of Treatment
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10 391 Figure 3. BA/CA ratio from Treatment to Final Height
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12 392 Figure 4. Height velocity from Treatment to Final Height – Individual patients shown. Solid bold
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14 393 line is average.
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Figure 1:



419 Figure 2.

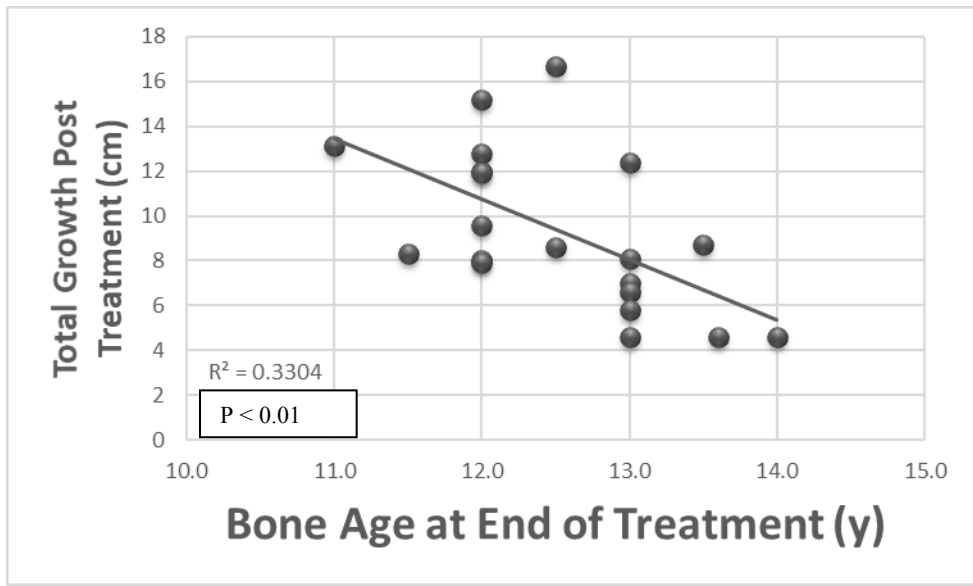


Figure 3.

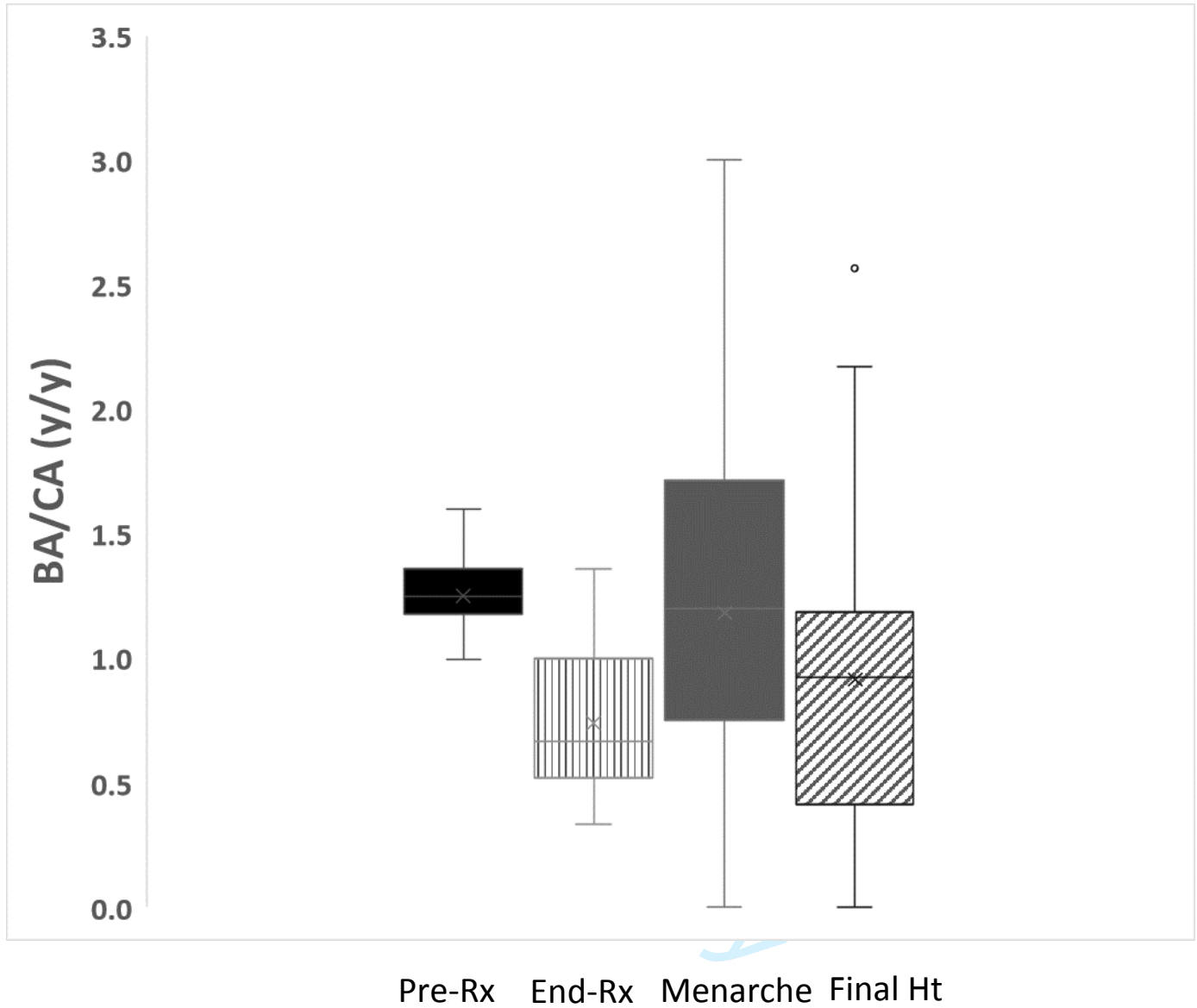
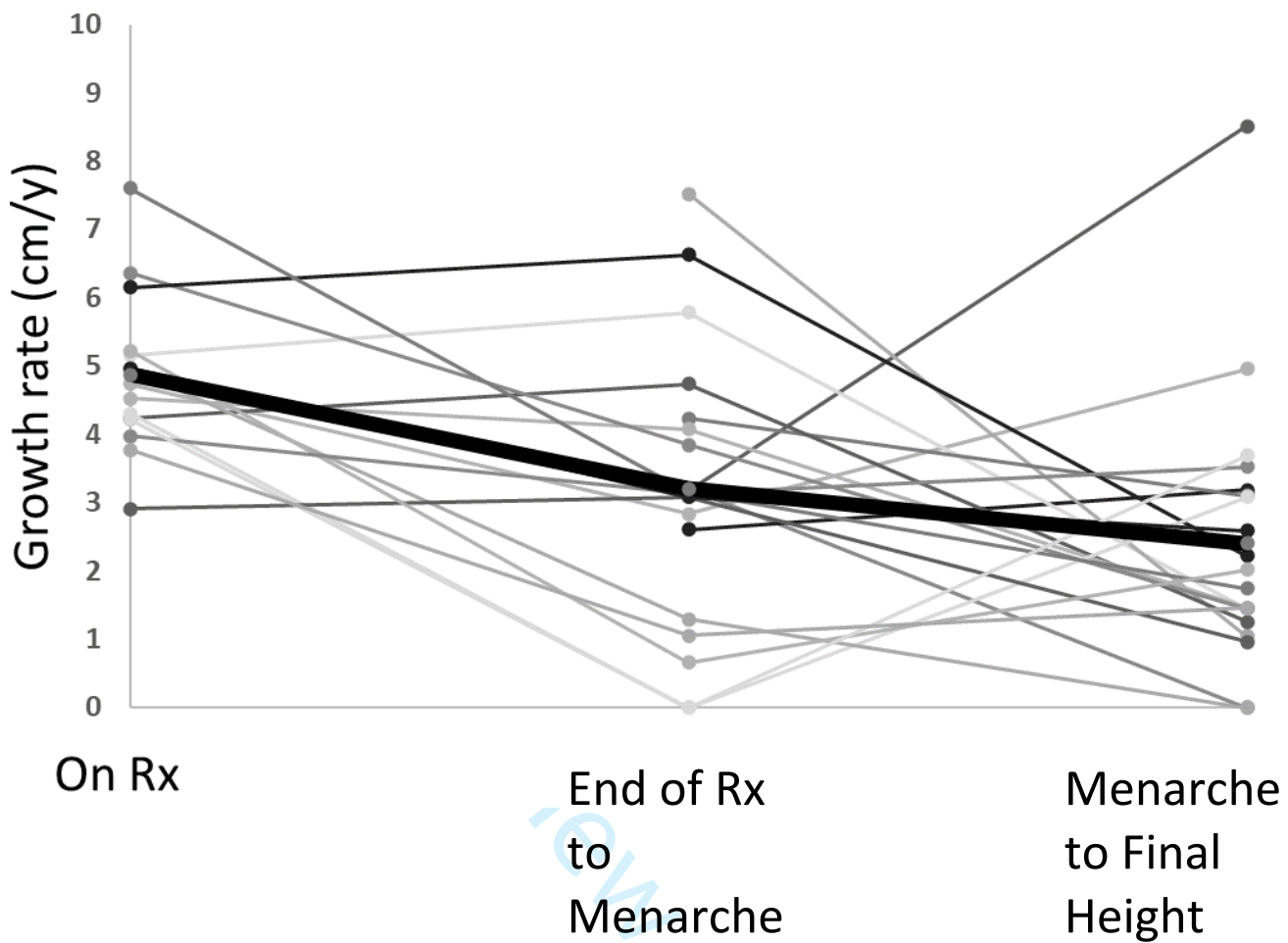


Figure 4.

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**No Pubertal Growth Spurt, Rapid Bone Maturation, and Menarche Post GnRHa
Treatment in Girls with Precocious Puberty**

Running Title:

Growth and Menses in CPP

Audrey Briscoe, Katherine Chen, Karen O. Klein

Division of Pediatric Endocrinology, Rady Children's Hospital San Diego, San Diego, and
Department of Pediatrics, Division of Pediatric Endocrinology, University of California San
Diego, San Diego, CA 92103, USA

Corresponding author:

Karen O. Klein, MD
3020 Children's Way, MC 5103
San Diego, CA 92123
Tel: 858-966-4032
Fax: 858-966-6227

ORCID ID - **0000-0002-7953-4691**

e-mails: kklein@ucsd.edu; audrey.briscoe@kp.org; katherinechen97@gmail.com

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3 31 **Abstract**
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8 33 *Objective* To study total growth, rate of bone maturation and menarche after discontinuation of
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10 34 Gonadotropin releasing hormone agonist (GnRHa) treatment for central precocious puberty
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12 35 (CPP).
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14 36 *Methods* Twenty girls with CPP on treatment with GnRHa were followed from discontinuation
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16
17 37 of treatment to final height (FH). Height, height velocity (HV), and bone age were measured
18
19 38 every 6 months. Age at menarche was collected.
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21 39 *Results* Once treatment is discontinued, rate of bone maturation (bone age [BA]/chronological
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23 40 [CA]) accelerated from 0.7 ± 0.3 at end of treatment to 1.2 ± 0.8 post treatment, similar to
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25 41 BA/CA prior to treatment. BA at treatment discontinuation ranged from 11 – 14 years. On
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27 42 average, treatment was stopped when CA was within 9 months of BA.
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31 43 All girls continued to grow from end of treatment to menarche averaging an increase of 4.7 ± 3.7
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33 44 cm, with HV 3.2 ± 2.0 cm/y. Post-menarche they grew an additional 4.6 ± 2.1 cm, with HV $2.4 \pm$
34
35 45 1.9 cm/y. Acceleration of HV was not seen post treatment. The younger the BA at initiation or
36
37 46 completion of treatment, the longer time to menarche. No one had menarche prior to a BA of
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39 47 12.5 y.
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41

42 48 *Conclusion* A pubertal growth spurt does not usually occur after treatment with GnRHa in girls
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44 49 with CPP. Rate of bone maturation accelerates post treatment. These factors are important in
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46 50 assessing optimal height outcome and decisions regarding cessation of treatment. This study will
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48 51 help clinicians give patients and families better estimates of growth and onset of menarche post
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50 52 treatment.
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54 **Introduction**

55 Gonadotropin releasing hormone agonist (GnRHa) treatment is standard of care for central
56 precocious puberty (CPP) (1-4). The treatment slows or halts pubertal progression, slows the rate
57 of bone maturation, suppresses gonadotropins, and usually decreases height velocity (HV) to
58 normal pre-pubertal levels. Predicted adult height (PAH) continues to improve while on
59 treatment, and then slowly decreases post treatment as rapid bone maturation resumes.
60 The decision regarding when to stop treatment needs to be individualized (5) and is based on
61 multiple factors. These include the child reaching an appropriate age for mid-puberty to resume
62 and a PAH reasonable for genetic potential, with caution that PAH may decrease once treatment
63 is discontinued (6). After discontinuation of GnRHa, the pubertal growth spurt typically does
64 not resume, however growth will continue at a slower velocity until cessation of growth. This
65 emphasizes the importance of not stopping treatment prematurely, as the remaining growth may
66 be minimal. There are limited studies of growth and HV after discontinuation of GnRHa,
67 especially as related to onset of menses (7). We studied rate of bone maturation and growth after
68 GnRHa treatment was stopped. We hypothesized that HV will not accelerate after treatment is
69 discontinued, and rate of bone maturation will accelerate. These results are helpful to parents
70 anticipating pubertal development, growth and menses post treatment, and provide important
71 information for the physician when deciding how long to continue GnRHa treatment based on
72 anticipated growth and menarche post treatment.

77 **Materials and Methods**

78 *Study population*

79 All girls in our pediatric endocrinology clinic (Rady Children's Hospital, San Diego, CA) who
80 were treated with the GnRHa Lupron Depot Ped (8,9) for CPP were offered participation in this
81 study once ready to discontinue treatment. Recruitment took place between 2009 – 2012, and
82 study follow-up visits were completed by 2016 once all girls reached final height. Determination
83 of treatment cessation was based on physician judgement and parent request. Twenty-one girls
84 agreed to participate. One girl dropped out prior to end of growth. One girl did not return for
85 confirmatory end of growth height measure, but was included as last two height measures were
86 within 0.7 cm and bone age was 15 years. We suspect that follow up was so consistent because
87 these girls were treated in our clinic by one provider for many years and were thankful for
88 continued care. All girls and their parents signed an assent and consent approved by our
89 institutional review board. All authors complied with the World Medical Association Declaration
90 of Helsinki regarding ethical conduct of research involving human subjects.

91 Girls were included if chronological age (CA) at onset of pubertal symptoms was less than 8
92 years old, breast development was consistent with at least pubertal stage 2 at diagnosis, bone age
93 (BA) was more than 2 SD above the mean for CA or PAH was at least 2 inches (5.08 cm) below
94 midparental height (MPH). Pubertal stage was defined according to a modification of Tanner's
95 description (10) to include breast palpation. Two patients were included without definitive data
96 on onset of breast development. Patient #8 is included even though age at onset of CPP is listed
97 at 8 y 4 m. This was by parent report of noticing breasts, however, since no physician saw her
98 prior to that time and breast stage was already fully stage 3 with BA 3 years advanced, we
99 suspect pubertal onset was likely prior to age 8 years. Patient #1 presented with menarche at 8 y

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3 100 10 m, She had stage 4 breast and a report that breast had been present since birth. Her BA was 3
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5 101 years advanced, so likely onset of CPP was less than 8 years old.
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7 102 CPP was defined as a peak LH level above 5 IU/L during an aqueous leuprolide stimulation test.
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10 103 All girls had idiopathic central precocious puberty. Girls were excluded if they had any other
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12 104 condition interfering with growth, such as skeletal dysplasia, cerebral palsy, or a chronic illness
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14 105 requiring treatment that may have impacted their growth potential. Stable patients with
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16 106 intermittent asthma or patients on topical acne medication were included.
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23 *Study design*

24 109 Girls underwent a general clinical examination and pubertal staging every 6 months until final
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26 110 height (FH) was reached. At each visit, height (using a Holtain stadiometer) and weight were
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28 111 recorded. The bone maturation was assessed with a left hand radiograph (BA), interpreted by one
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30 112 of two blinded investigators (AB, KK) according to the Greulich and Pyle method (11). There
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32 113 were no differences in readings between investigators on 20 independently read images. PAH
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34 114 was calculated at each visit according to Bailey-Pineau tables (11). All girls participating in the
35
36 115 study had a BA x-ray obtained every 6 months. Growth was considered complete when 3
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38 116 consecutive heights were all within 0.5 cm ($HV \leq 0.5$ cm/yr), to ensure no further growth from
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40 117 measurement error. Girls were asked to record all menstrual cycles in detail in a calendar, with
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42 118 duration, severity, and timing noted.
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48 *Statistical analysis*

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51 121 All data is presented as mean \pm SD. Linear regression analysis was used for correlations. MPH
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53 122 was calculated with parental report of height at the first visit; MPH=[maternal height
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3 123 (cm)+paternal height(cm)-13]/2. MPH was available for 19/20 subjects. Height velocity was
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5 124 calculated based on the data as cm per year change (cm/y).
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8 125 Rate of change of BA was calculated as the change in BA in years divided by time interval to
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10 126 yield a change in units of year per chronological year (y/y).
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15 128 **Results**

16
17 129 Twenty girls remained in the study until FH was reached. Baseline characteristics are shown in
18
19 130 Table 1, 2 and 3. GnRHa treatment was stopped at an average age of 11.8 ± 0.6 years (range
20
21 131 10.6 – 13.2 years). Girls were treated for an average duration of 4.5 ± 2.4 years (range 1.5-10.4
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23 132 years). The average reported age at onset of puberty was 5.8 ± 2.1 years (range 1.0 - 8.4 years).
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25 133 One girl was included in the study who had her onset of puberty estimated by parents at 8.4
26
27 134 years, however she had rapid progression of puberty, her BA was 2 years advanced, and her
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29 135 PAH was below her MPH.
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33 136 34 35 137 *Bone maturation*

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37 138 BA at discontinuation of treatment ranged from 11 – 14 years (average 12.5 ± 0.8 years). The
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39 139 BA at the onset and end of treatment both had a negative correlation with time to menarche post
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41 140 treatment ($p < 0.01$). Girls with a younger BA at onset or end of treatment developed menarche
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43 141 later than girls with an older BA at either time point during treatment ($p < 0.01$)(Figure 1). BA at
44
45 142 end of treatment also had a negative correlation with the amount of growth accrued post
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47 143 treatment, such that the younger the BA at end of treatment, the greater overall growth post-
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49 144 treatment ($p < 0.01$)(Figure 2). No one had menarche prior to a bone age of 12.5 y.
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3 145 The rate of change of BA advancement averaged 1.3 ± 0.15 prior to treatment, and decreased
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5 146 during treatment to 0.7 ± 0.3 years per chronological year (y/y). Post treatment, rate of BA
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7 147 change accelerated to 1.2 ± 0.8 y/y (range 0 – 3.0y/y). (Table 2, Figure 3).

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10 148 On average, treatment was stopped when CA was within 9 months of BA. Three girls had a BA
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12 149 > 2 year beyond CA at end of treatment. They also had the 3 oldest BA at the end of treatment,
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14 150 but 2 girls surpassed their MPH (1 did not have MPH available).

151 152 *Growth*

153 Average HV on treatment was 4.8 ± 1.2 cm/y (range 2.9 - 7.6). All girls continued to grow from end
154 of treatment to menarche with an average of 4.7 ± 3.7 cm, with an average height velocity of $3.2 \pm$
155 2.0 cm/y. On average, they grew an additional 4.6 ± 2.1 cm from menarche until FH, with a HV
156 of 2.4 ± 1.9 cm/y during that time. (Fig 4) Only 2/20 girls, had an increased height velocity (>6
157 cm/yr) after treatment was discontinued, similar to a pubertal height velocity. Growth after
158 discontinuation of treatment ranged from 4.6 – 12.4 cm in girls who stopped GnRHa with a BA \geq
159 13 years, and 7.9 – 16.7 cm in girls who stopped GnRHa with a BA < 13 years.

160 161 *Menarche*

162 After treatment was discontinued, the average age at menarche was 13.2 ± 0.9 years, however
163 ranged from 11.3 – 14.6 years. The average time from end of treatment to menarche was $15.2 \pm$
164 7.4 months, with a range of 3 – 30 months. The younger the BA was at initiation or completion
165 of treatment, predicted a longer time to menarche. Menses occurred at regular intervals (defined
166 as cycles 21 – 35 days long) in some girls immediately post treatment, although other girls
167 continued to have irregular menses up to 3 years post treatment. No predictions of time to

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3 168 regular menstrual cycles were found. When data was analyzed to compare girls with onset of
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5 169 $CPP \leq 6$ yo compared to those > 6 yo, the only significant difference, other than the obvious age
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8 170 and BA, was age at onset of menarche. The younger girls had menarche on average one year
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10 171 later than the older girls, but at a similar BA.

14 15 173 *Adult final height*

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17 174 FH occurred an average of 2 years post menarche, with a range of 0 to 3.7 years. FH was within
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19 175 3 inches of MPH in 18/19 (1 child without MPH data) girls. Average difference between MPH
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21 176 and FH (MPH-FH) was 0.5 ± 6.0 cm. MPH was reached or surpassed by 11/19 (58%) girls
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23 177 treated with GnRHa for CPP. One girl attained a FH 14 cm below MPH, however her parents
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25 178 were tall (MPH =170 cm), pubertal onset was quite early at 5.5 years and her BA was 3.75 years
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27 179 advanced at start of treatment. Another girl attained a FH quite below her MPH, however she
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29 180 also had 2 tall parents (MPH = 176.5 cm) and onset of puberty at age 1.5 years old, although was
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31 181 able to reach a FH of 168 cm (Table 3).

34 35 182 36 37 183 **Discussion**

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39 184 Time to menarche is a great concern for many children and their families. The range of onset of
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41 185 menarche post GnRHa treatment is consistent across studies (12-15) from 3 months to 3 years.
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43 186 The present study confirms that range but shows for the first time the relationship between BA
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45 187 and menarche. We found that the younger the BA was prior to treatment or the younger the BA
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47 188 was at the end of treatment, predicted a longer time to menarche. No girls had menarche prior to
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49 189 BA of 12.5 years. When girls were compared by onset of $CPP \leq 6$ years versus > 6 yo, the
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51 190 younger girls had menarche on average one year later than the older girls, but at a similar BA.
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3 191 This supports the importance of BA in predicting menarche. There were no other differences
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5 192 between these 2 groups, supporting the robustness of this population with truly rapidly
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7 193 progressing CPP, rather than a mixed population of early normal puberty and CPP. This is one
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9 194 of the strengths of the population, since many publications likely include some early normal
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11 195 puberty when girls close to 8 years old are studied.
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17 197 Rate of BA advancement prior to treatment in girls with CPP is accelerated. On GnRHa
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19 198 treatment, rate of advancement slows to less than 1 year per year when treatment is optimal, and
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21 199 therefore leads to increases in growth potential and FH (20). Once treatment is stopped, we
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23 200 suspected that rate of BA advancement accelerates, and this is the first study with data to support
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25 201 that pathophysiology. Prior to GnRHa treatment rate of BA advancement in this population on
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27 202 average was 1.3 years per chronological year (5). This decreases to an average of 0.7 years per
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29 203 year on treatment. Post treatment, rate of BA advancement accelerates back to pretreatment rapid
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31 204 maturation averaging 1.2 years per year. This is expected since whatever process causes rapid
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33 205 bone maturation in CPP, is not cured by GnRHa treatment, but rather slowed down during
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35 206 treatment. Lazar et al (21) reported data from 115 girls post-GnRHa treatment. They describe
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37 207 greater height gain post treatment in girls who had onset of puberty prior to 6 years old compared
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39 208 to older girls. Final height in the older groups was less than PAH at end of treatment. They
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41 209 measured BA every 12 months and report that BA at end of treatment significantly contributed to
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43 210 prediction of height gain post treatment. However, they do not report change in BA post
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45 211 treatment. They raised the question of whether post-treatment growth would have been greater if
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47 212 BA was closer to 11 at end of treatment. The present data support the opposite hypothesis, since
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49 213 rate of BA advance accelerates post treatment, stopping treatment at an older BA may lead to
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3 214 greater final height, achieved by more growth on treatment rather than more growth post-
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5 215 treatment. Shim et al also looked at growth post-GnRHa treatment in 85 boys but compared only
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7 216 PAH at end of treatment to final height, and did not delineate BA or growth rate changes over
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9 217 the years post treatment (22).
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14 219 On average, treatment was stopped when CA was close to BA. Adequate pubertal suppression
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16 220 with GnRHa theoretically corrects the discrepancy between BA and CA seen prior to treatment.
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18 221 The girls in this study who did not reach a CA within 2 years of BA prior to end of treatment,
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20 222 were treated until an older BA than the rest of the girls, which was likely necessary to achieve
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22 223 improved FH outcomes. This supports the likely the importance of duration of treatment for
23
24 224 optimal height outcome. Of course, we cannot know what height the girls would have achieved
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26 225 if treatment had been discontinued earlier, but we have shown the rapid acceleration of rate of
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28 226 bone maturation post treatment so it would be unlikely they would have reached the same FH.
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30 227 Previous studies showed that earlier onset of treatment, less BA advancement, and less delay
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32 228 from onset of CPP to onset of treatment have taller height outcomes as compared to MPH (6,16-
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34 229 19). In the present study, girls with less BA advancement had greater growth post treatment.
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36 230 This is the first study to quantify growth and growth rate between end of treatment and menarche
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38 231 and between menarche and FH. This is very important for clinicians and families when making
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40 232 decisions about the timing for cessation of GnRHa treatment. Those decisions cannot be based
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42 233 on expectations for resumption of a pubertal growth spurt post treatment. Only 2 girls in this
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44 234 population had increased HV to > 6 cm/y post treatment. All others grew at ≤ 5 cm/y after
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46 235 GnRHa was stopped. An interrupted pubertal growth spurt does not resume post GnRHa
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48 236 treatment for CPP.
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5 238 The lack of rapid pubertal growth post treatment is likely related to growth plate senescence. Our
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8 239 understanding of growth plate senescence includes the effect of estrogen to first stimulate growth
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10 240 plate chondrogenesis and therefore linear growth, while simultaneously decreasing the number of
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12 241 resting zone chondrocytes, accelerating the rate of chondrocyte proliferation leading to earlier
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14 242 proliferative exhaustion with eventual growth plate fusion (23,24). The early exposure of
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16 243 estrogen in precocious puberty causes early growth plate senescence. Perhaps GnRHa treatment
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18 244 is usually timed to interrupt this process at the point when estrogen has already diminished
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20 245 enough chondrocytes, such that as bone aging continues during treatment and no further increase
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22 246 is possible post treatment. The older the BA was at the beginning of treatment, the less growth is
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24 247 accrued post treatment. We can interrupt the process of CPP causing rapid maturation of BA, but
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26 248 the process of senescence, although slowed during treatment, is not stopped, so we cannot regain
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28 249 all the growth potential that was lost. This is further support of continuation of GnRHa longer in
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30 250 those girls with late onset of treatment who have short height potential compared to MPH.
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32 251 It cannot be determined from this study whether growth would have been different if treatment
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34 252 was stopped earlier in the girls with more advanced BA. However, in all girls HV was good
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36 253 throughout treatment, there was similar amount of growth post treatment, and height outcomes
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38 254 compared to MPH were similar across all girls. This suggests that the individual treatment
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40 255 decisions of when to stop GnRHa treatment led to the best expected outcomes.
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42 256 The girls in this study were all treated until almost 11 yo or more in order to maximize height
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44 257 benefit as well as have their physical findings of puberty coincide with their peers. When the
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46 258 primary goal of treatment is prevention of early menarche, treatment is often discontinued
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48 259 between 10 – 11 yo, anticipating onset of menarche on average 18 months post treatment. While
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3 260 not the focus of this study, the cost-implications of continuing treatment should always be kept in
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5 261 mind (25). Aside from cost-implications, however, the range of onset of menarche is 3 months to
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7 262 2.5 years post treatment, similar to other published studies. Therefore, the older age at
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10 263 discontinuation in this cohort is unlikely to have affected the results of time to menarche or
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12 264 growth post treatment. It is always clinically relevant to inform families that a 10 yo girl who
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14 265 stops treatment may have menarche by 10 years 3 months, which would still be quite early after
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17 266 years of treatment to delay menarche.”

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19 267 The major strengths of this study include following girls to FH with measures of growth, bone
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21 268 maturation and menses every 6 months for as long as 5 – 6 years post GnRHa treatment. This
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23 269 study also has girls who continued GnRHa until 13 – 14 years with good growth during the
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25
26 270 treatment interval, as well as post treatment. We found that 18/19 had FH within 3 inches of
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28 271 MPH, with more than half of the girls reaching or surpassing MPH. The wide range of age at
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30 272 onset of puberty allowed assessment of age as a factor contributing to timing of menarche.
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35 274 The major limitations include the small number of participants, although this does show a real-
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37 275 world example from one center. All girls were offered participation, but not all girls wanted to
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39 276 continue to be followed every 6 months once treatment was discontinued, so there may have
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42 277 been some bias in those who continued coming. For example, those who did not continue follow
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44 278 up may have been obviously growing less and therefore not interested in continued bone age to
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47 279 assess potential growth. It is unlikely that those who preferred not to continue were those
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49 280 growing more rapidly, but that cannot be determined. Another limitation is that bone age at
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51 281 cessation of treatment was not randomized, so physician decisions to stop treatment could bias
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3 282 outcomes. However, it would not be ethical to randomize treatment cessation if physician
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5 283 assessment indicated possible benefit to continued treatment.
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10 285 In conclusion, the present study quantitates growth after treatment with GnRHa in girls with
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12 286 CPP. In most girls, there is no resumption of pubertal growth spurt post GnRHa treatment. Time
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14 287 to onset of menarche post-GnRHa treatment is proportionate to BA at the start as well as the end
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16 288 of treatment, with no girls in the present study having menarche prior to BA of 12.5 years. Since
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18 289 time to menarche post treatment is multifactorial and not yet able to be predicted, this study adds
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20 290 some guidelines and suggests continuation of treatment beyond a bone age of 12.5 years in
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22 291 younger girls, where earlier menarche continues to be a concern. Rate of bone maturation
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24 292 accelerates post treatment. These factors are important in assessing potential height outcome and
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26 293 the decision regarding timing for cessation of treatment. This study will help clinicians give
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28 294 patients and families better estimates of growth and onset of menarche post treatment.
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54 304 **References**

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- 1
2
3 305 1. Eugster EA. Precocious Puberty. *J Clin Endocrinol Metab* 2006; - 91(9); 15A-16A
4
- 5 306 2. Pace JN, Miller JL, Rose LI. GnRH agonists: gonadorelin, leuprolide and nafarelin. *Am Fam*
6
7
8 307 *Physician*. 1991; Nov; 44(5):1777-82.
- 9
10 308 3. Kaplan SL, Grumbach MM. Clinical Review 14: Pathophysiology and treatment of sexual
11
12 309 precocity. *J Clin Endocrinol Metab* 1990; 71:785–789
- 13
14 310 4. Conn PM, Crowley WF. Gonadotropin-releasing hormone and its analogs. *Annu Rev Med*
15
16 311 1994; 45:391–405
- 17
18 312 5. Vargas Trujillo M, Dragnic S, Aldridge P, Klein KO. Importance of individualizing treatment
19
20 313 decisions in girls with central precocious puberty when initiating treatment after age 7 years or
21
22 314 continuing beyond a chronological age of 10 years or a bone age of 12 years. *J Pediatr*
23
24 315 *Endocrinol Metab*. 2021 Apr 15;34(6):733-739.
- 25
26 316 6. Klein KO, Barnes KM, Jones JV, Feuillan PP, Cutler, GB. Increased Adult Height in
27
28 317 Precocious Puberty after Long-Term Treatment with LHRH Agonists: The National Institutes of
29
30 318 Health Experience *J Clin Endocrinol Metab* 2001; 86: 4711 – 4716
- 31
32 319 7. Carel JC, Roger M, Ispas S, Tondu F, Lahlou N, Blumberg J, et al. Final height after long-
33
34 320 term treatment with triptorelin slow release for central precocious puberty: importance of statural
35
36 321 growth after interruption of treatment. French study group of Decapeptyl in Precocious Puberty.
37
38 322 *J Clin Endocrinol Metab* 1999;84:1973-8.
- 39
40 323 8. Wilson AC, Meethal SV, Atwood CS. Leuprolide acetate: a drug of diverse clinical
41
42 324 applications *Expert Opin Investig Drugs*. 2007 Nov; 16(11):1851-63.
- 43
44 325 9. Kappy MS, Stuart TE, Perelman AH, Clemons RD. Suppression of gonadotropin acetate by a
45
46 326 long-acting gonadotropin-releasing hormone analog (leuprolide acetate, Lupron depot) in
47
48 327 children with precocious puberty. *J Clin Endocrinol Metab* 1989; 69:1087–1089
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51
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- 1
2
3 328 10. Tanner JM. Growth at adolescence. 1966; 2nd ed. New York, NY: Appleton-Century-Crofts
4
5 329 11.. Greulich WW, Pyle SI. 1959 Radiographic Atlas of Skeletal development of the hand and
6
7 330 Wrist, 2nd Ed. Stanford, CA: Stanford University Press
8
9 331 12. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Group E-LGACC, et al.
10
11 332 Consensus statement on the use of gonadotropin-releasing hormone analogs in children.
12
13 333 Pediatrics 2009;123:e752-62.
14
15 334 13. Guaraldi F, Beccuti G, Gori D, Ghizzoni L. Management of endocrine disease: long-term
16
17 335 outcomes of the treatment of central precocious puberty. Eur J Endocrinol 2016;174:R79-87.
18
19 336 14. Poomthavorn P, Suphasit R, Mahachoklertwattana P. Adult height, body mass index and time
20
21 337 of menarche of girls with idiopathic central precocious puberty after gonadotropin-releasing
22
23 338 hormone analogue treatment. Gynecol Endocrinol 2011;27:524-8.
24
25 339 15. Neely EK, Lee PA, Bloch CA, Larsen L, Yang D, Mattia-Goldberg C, et al. Leuprolide
26
27 340 acetate 1-month depot for central precocious puberty: hormonal suppression and recovery. Int J
28
29 341 Pediatr Endocrinol 2010;2010:398639.
30
31 342 16. Mul D, Oostdijk W, Otten BJ, Rouwe C, Jansen M, Delemarre-van de Waal HA, et al. Final
32
33 343 height after gonadotrophin releasing hormone agonist treatment for central precocious puberty:
34
35 344 the Dutch experience. J Pediatr Endocrinol Metab 2000;13 Suppl 1:765-72.
36
37 345 17. Partsch CJ, Heger S, Sippell WG. Treatment of central precocious puberty: lessons from a 15
38
39 346 years prospective trial. German Decapeptyl Study Group. J Pediatr Endocrinol Metab 2000;13
40
41 347 Suppl 1:747-58.
42
43 348 18. Styne DM, Harris DA, Egli CA, et al. Treatment of true precocious puberty with a
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3 349 potent luteinizing hormone-releasing factor agonist: effect on growth, sexual maturation, pelvic
4
5 350 sonography, and the hypothalamic-pituitary-gonadal axis. *J Clin Endocrinol Metab.* 1985;
6
7 351 61:142–151
- 8
9
10 352 19. Brito VN, Latronico AC, Cukier P, Teles MG, Silveira LF, Arnhold IJ, Mendonca BB.
11
12 353 Factors determining normal adult height in girls with gonadotropin-dependent precocious 20.
13
14 354 Lazar L, Kuali R, Pertzalan A, Phillip M. Gonadotropin-suppressive therapy in girls with early
15
16 355 and fast puberty affects the pace of puberty but not total pubertal growth or final height. 2002;
17
18 356 87(5):2090-2094.
- 19
20
21 357 21. Lazar L, Padoa A, Phillip M. Growth pattern and final height after cessation of gonadotropin-
22
23 358 suppressive therapy in girls with central sexual precocity. 2007; 92(9):3483-3489.
- 24
25
26 359 22. Shim YS, Lim KI, Lee HS, Hwang JS. Long-term outcomes after gonadotropin-releasing
27
28 360 hormone agonist treatment in boys with central precocious puberty. 2020;PLoS ONE
29
30 361 15(12):e0243212
- 31
32
33 362 puberty treated with depot gonadotropin-releasing hormone analogs. *J Clin Endocrinol Metab.*
34
35 363 2008; Jul;93(7):2662-9
- 36
37
38 364 23. Lui JC, Nilsson O, Baron J. Recent research on the growth plate: Recent insights into the
39
40 365 regulation of the growth plate. *Journal of molecular endocrinology.* 2014;53(1):T1–9. Epub
41
42 366 2014/04/18. 10.1530/JME-14-0022
- 43
44
45 367 24. Weise M, De-Levi S, Barnes KM, Gafni RI, Abad V, and Baron J. Effects of estrogen on
46
47 368 growth plate senescence and epiphyseal fusion. *Proc Natl Acad Sci U S A.* 2001 Jun 5; 98(12):
48
49 369 6871–6876.
- 50
51
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55
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370 25. Kaplowitz PB, Backeljauw PF, Allen DB. Toward more targeted and cost-effective
 371 gonadotropin-releasing hormone analog treatment in girls with central precocious puberty. *Horm*
 372 *Res Paediatr* 2018;90(1):1-7

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374 Table 1. Patient age and time to menarche

<u>Patient ID</u>	<u>Ethnicity</u>	<u>CA at onset CPP</u>	<u>CA at start Rx</u>	<u>CA at stop Rx</u>	<u>Duration of Rx (y)</u>	<u>CA at Menarche</u>	<u>Time post Rx to Menarche (months)</u>	<u>Time menarche to FH (y)</u>
20	White	1.5	1.5	11.2	9.7	13.5	28.0	0.7
9	Hispanic	5.0	8.8	12.8	4.0	13.6	11.0	1.2
18	Hispanic	7.5	8.0	11.0	3.0	13.5	30.0	0.0
6	White	7.5	7.5	11.3	3.8	12.3	12.0	2.2
12	White	5.6	6.6	11.6	5.0	13.3	22.0	3.2
19	Asian	6.6	7.8	11.8	4.0	13.2	16.4	1.6
21	Hispanic	1.0	1.6	12.0	10.4	14.2	26.4	1.1
5	White	7.0	8.2	12.1	3.9	13.8	20.0	3.2
15	White	5.9	7.3	13.3	6.0	14.6	16.2	1.7
3	White	7.8	9.3	11.8	2.5	12.6	10.0	3.7
10	White	2.4	3.8	12.5	8.7	14.2	19.0	2.8
4	White	6.0	8.9	11.5	2.6	13.9	5.0	2.3
16	White	5.5	6.3	11.7	5.4	13.0	16.0	0.0
2	White	7.3	8.5	11.9	3.4	12.3	8.0	2.6
7	Hispanic	7.0	7.8	12.0	4.2	13.2	14.0	2.3
11	Hispanic	6.0	8.5	12.6	4.1	13.6	11.0	2.0
17	Hispanic	5.0	8.6	12.6	4.0	13.8	13.8	2.5
1	Hispanic	*	9.2	10.7	1.5	11.3	7.0	2.7
13	White	7.4	8.8	11.3	2.6	11.6	3.0	1.2
8	Asian	8.4	9.3	11.5	2.2	12.8	16.0	2.2
Average		5.8	7.3	11.8	4.5	13.2	15.2	2.0
Minimum		1.0	1.5	10.7	1.5	11.3	3.0	0.0
Maximum		8.4	9.3	13.3	10.4	14.6	30.0	3.7
SD		2.1	2.3	0.6	2.4	0.9	7.4	1.0

* menarche at 8.8, but breast onset not known

BA = bone age, Rx = treatment, FH = final height, CA - chronological age, CPP = central precocious puberty

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379 Table 2. Bone age data during and after treatment with GnRHa

Patient ID	BA start Rx (y)	BA/CA start Rx	BA end of Rx (y)	BA at menarche (y)	BA at FH (y)	BA/CA during Rx	BA/CA end Rx to menarche	BA/CA menarche to FH
20	**	**	11.0	15.0	15.0	**	1.7	0.0
9	8.8	1.0	11.5	13.5	16.0	0.7	2.2	2.2
18	10.0	1.3	12.0	16.5	16.8	0.7	1.8	0.5
6	**	**	12.0	15.0	15.0	**	3.0	0.0
12	6.8	1.0	12.0	12.5	16.5	1.0	0.3	1.3
19	7.8	1.0	12.0	13.8	15.5	1.1	1.3	1.1
21	2.0	1.3	12.0	15.0	15.5	1.0	1.4	0.4
5	***	***	12.0	13.5	17.0	***	0.9	1.1
15	10.0	1.4	12.0	14.0	16.3	0.3	1.5	1.4
3	11.0	1.2	12.5	13.8	***	0.6	1.5	***
10	4.6	1.2	12.5	14.0	16.5	0.9	0.9	0.9
4	12.0	1.3	13.0	16.0	17.0	0.4	1.23	0.4
16	10.0	1.6	13.0	***	***	0.6	***	***
2	11.0	1.3	13.0	13.0	16.0	0.6	0.0	1.2
7	11.0	1.4	13.0	14.3	15.0	0.5	1.1	0.3
11	11.0	1.3	13.0	15.0	15.5	0.5	2.2	0.3
17	10.0	1.2	13.0	13.0	15.8	0.8	0.0	1.1
1	11.5	1.3	13.5	13.5	16.0	1.4	0.0	0.9
13	12.0	1.4	13.6	13.8	17.0	0.6	0.8	2.6
8	11.5	1.2	14.0	15.0	17.0	1.1	0.8	0.9
Average	9.5	1.3	12.5	14.2	16.1	0.7	1.2	0.9
Minimum	2.0	1.0	11.0	12.5	15.0	0.3	0.0	0.0
Maximum	12.0	1.6	14.0	16.5	17.0	1.4	3.0	2.6
SD	2.8	0.2	0.8	1.0	0.7	0.3	0.81	0.7

** came to us on treatment without records

*** missing data

BA = bone age, Rx = treatment, FH = final height, CA - chronological age

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383 Table 3. Growth changes during and after treatment with GnRH α

<u>Patient ID</u>	<u>Ht start of Rx (cm)</u>	<u>Ht end Rx (cm)</u>	<u>Growth end Rx to menarche (cm total)</u>	<u>HV end Rx to menarche (cm/y)</u>	<u>Ht at menarche (cm)</u>	<u>FH (cm)</u>	<u>CA at FH (y)</u>	<u>Growth menses to FH (cm total)</u>	<u>HV menarche to FH (cm/y)</u>	<u>MPH (cm)</u>	<u>MPH - FH (cm)</u>
20	**	154.9	7.4	3.2	162.3	168.0	14.2	5.7	8.5	176.4	8.4
9	134.0	152.7	2.6	2.8	155.3	161.0	14.8	5.7	5.0	156.1	-4.9
18	141.7	162.5	8.0	3.2	170.5	170.5	14.0	0.0	0.0	168.5	-2.0
6	**	155.6	2.6	2.6	158.2	165.2	14.5	7.0	3.2	157.3	-7.9
12	114.5	140.3	10.6	5.8	150.9	155.5	16.4	4.6	1.5	155.1	-0.4
19	122.8	152.7	10.3	7.5	163.0	164.7	14.8	1.7	1.0	161.1	-3.6
21	80.5	152.7	9.3	4.2	162.0	165.5	15.3	3.5	3.1	171.3	5.8
5	125.0	141.4	7.9	4.7	149.3	153.3	17.0	4.0	1.3	161.1	7.8
15	119.7	146.6	5.5	4.1	152.1	154.5	16.3	2.4	1.5	162.4	7.9
3	147.5	163.4	3.2	3.8	166.6	172.0	16.3	5.4	1.4	171.3	-0.7
10	106.5	160.0	10.5	6.6	170.5	176.7	17.0	6.2	2.2	168.8	-7.9
4	142.3	153.5	0.0	0.0	153.5	160.5	16.2	7.0	3.1	152.3	-8.3
16	120.7	147.6	3.0	1.3	150.6	155.7	15.8	5.1	0.0	170.0	14.3
2	136.9	162.9	2.1	3.1	165.0	169.5	14.9	4.5	1.7	165.0	-4.6
7	130.5	142.7	3.6	3.1	146.3	148.5	15.5	2.2	1.0	156.1	7.6
11	127.4	148.7	0.6	0.7	149.3	153.3	15.6	4.0	2.0	158.6	5.3
17	124.3	140.2	3.6	3.1	143.8	152.6	16.3	8.8	3.5	153.5	0.9
1	135.0	142.3	1.8	3.1	144.1	151.0	13.9	6.9	2.6	***	***
13	140.8	151.7	0.0	0.0	151.7	156.3	12.8	4.6	3.7	152.9	-3.4
8	147.5	155.8	1.4	1.0	157.2	160.4	15.0	3.2	1.5	156.1	-4.3
Average	127.6	151.4	4.7	3.2	156.1	160.7	15.3	4.6	2.4	161.8	0.5
Minimum	80.5	140.2	0.0	0.0	143.8	148.5	12.8	0.0	0.0	152.3	-8.3
Maximum	147.5	163.4	10.6	7.5	170.5	176.7	17.0	8.8	8.5	176.4	14.3
SD	16.4	7.6	3.7	2.0	8.3	7.9	1.1	2.1	1.9	7.4	6.7

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3 ** came to us on treatment without records

4 *** missing data

5 HV = height velocity, Rx = treatment, FH = final height, CA -
6 chronological age, Ht – height, MPH = mid-parental height

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15 387 **Figure Legends**

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17 388 Figure 1: Time to Menarche post GnRHa treatment by bone age at start of treatment (A) and by
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19 389 bone age at end of treatment (B)

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22 390 Figure 2. Total Growth post GnRHa treatment by BA at end of Treatment

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24 391 Figure 3. BA/CA ratio from Treatment to Final Height

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26 392 Figure 4. Height velocity from Treatment to Final Height – Individual patients shown. Solid bold
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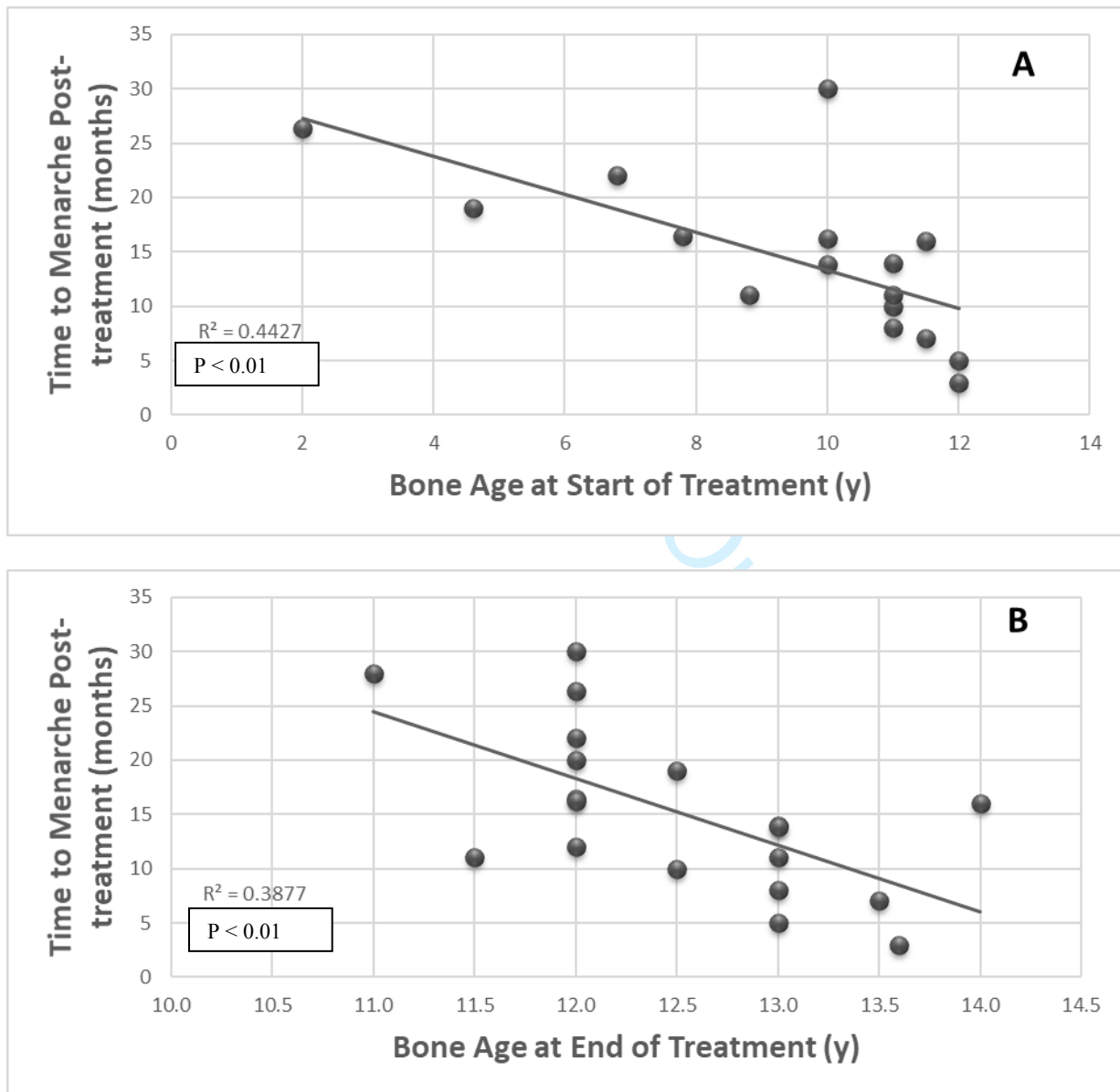
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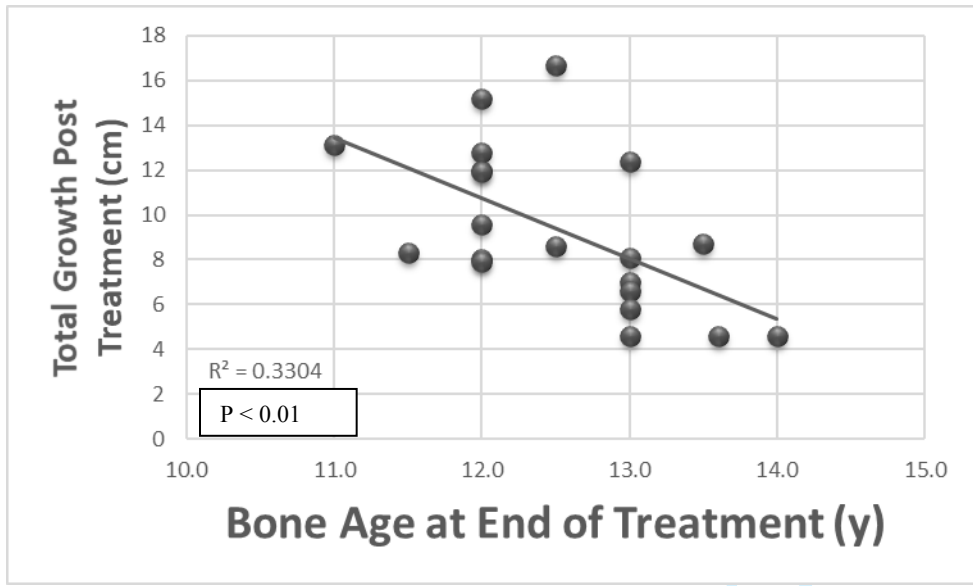
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Figure 1:



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435 Figure 3.

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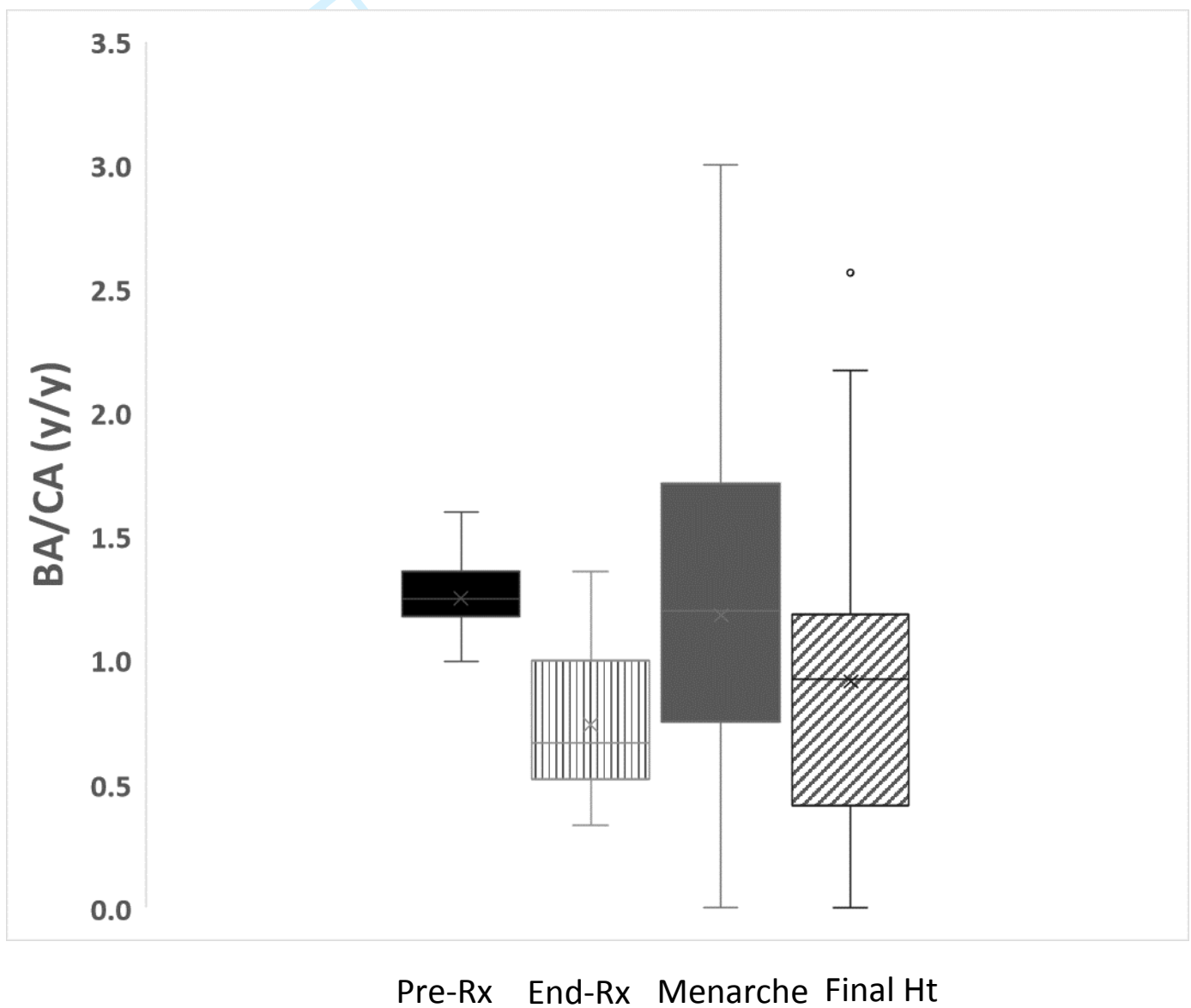
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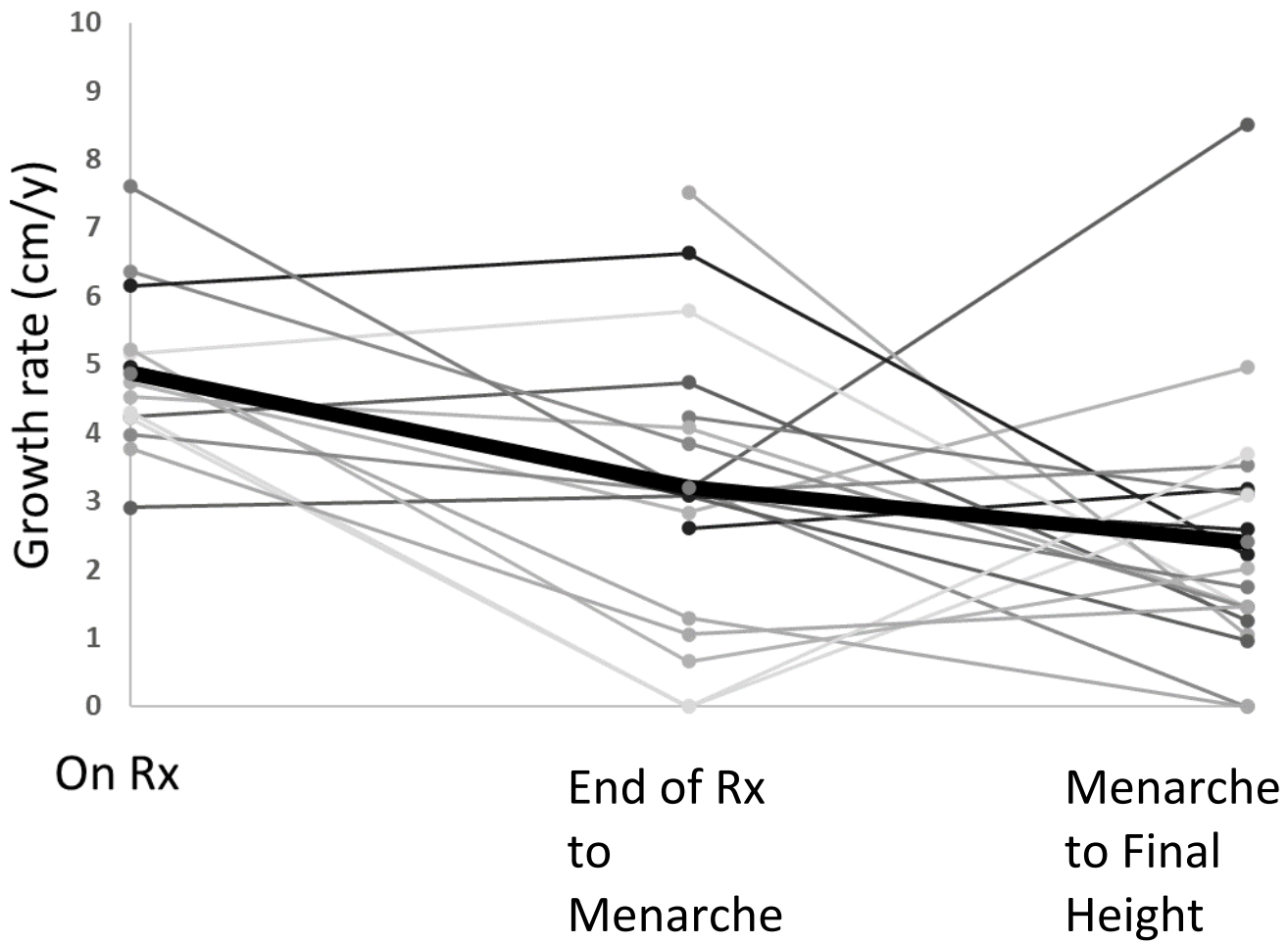
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Figure 4.



Strictly adhere to the given format!

In case informed consent or ethical approval do not apply the statements should read: "Not applicable".

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Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests

Karen Klein is a consultant for AbbVie Pharm, Arbor Pharm, and Tolmar Pharm. Audrey Briscoe and

Katherine Chen have nothing to disclose

Informed consent

Informed consent was obtained from all individuals included in this study.

Ethical approval

The local Institutional Review Board approved this study.