Time to Menarche after Completing Gonadotropin-Releasing Hormone Agonist in Girls with Central Precocious or Early-onset Puberty

Presentation Number
P2-D2-543

Shin-Hee Kim, In-Ah Jung, Won Kyoung Cho, Kyoung Soon Cho, So Hyun Park, Min Ho Jung*, Byoung Kyu Suh

Department of Pediatrics, The Catholic University of Korea School of Medicine, Seoul, Korea

***Correspondenace**
MIN HO JUNG, MD, PhD
TEL: +82-2-3779-1131
FAX: +82-2-783-2589
E-mail:jmhpe@catholic.ac.kr

Introduction

Children with central precocious puberty (CPP) prematurely develop pubertal pulsatile release of gonadotropin-releasing hormone (GnRH), leading to an increase in gonadotropin and sex steroid levels, development of secondary sexual characteristics, advancement of bone age (BA) and consequent reduction in adult height. Although the effect of GnRHa treatment has been evaluated by several investigators, limited data are available on the time to menarche after completing GnRHa in Korean girls with CPP or Early-onset puberty (EP).

Our aim was to evaluate the timing of menarche and the associated factors among patients with CPP or EP who were treated with GnRHa.

Patients and methods

We analyzed clinical and laboratory data of 98 girls (78 CPP and 20 EP) who were treated with GnRHa (Table 1). Cumulative incidence of menarche was calculated by Kaplan-Meier method. Clinical and laboratory parameters associated with time to menarche were determined using the Cox proportional hazards model.

Table 1. Clinical and laboratory parameters of patients

Charicteristic	Before treatment	At end of therapy	P value
Age	8.7 (8.2–9.3)	11.6 (11.2–11.9)	NA
Bone age	10.5 (10–11.5)	12 (11.5–12)	NA
Height	133 (128.1–137.2)	148.1 (144.6–152)	NA
Ht-SDS	0.73 (0.25–1.33)	0.14 (-0.41–0.74)	<0.001
Weight	31.5 (27–36)	45.3 (38.4–51)	NA
Weight-SDS	0.75 (0.06–1.35)	0.66 (-0.17–1.32)	0.007
BMI	17.6 (16.3–19.7)	20.7 (18.3–22.3)	NA
BMI-SDS	0.57 (-0.16–1.05)	0.78 (-0.009–1.18)	0.005
acPAH	150 (147.6–154.6)	160.4 (157.3–164)	NA
avPAH	155 (152.7–159.3)	164.3 (160.9–167)	NA
acPAH-SDS	-1.97 (-2.68– -1.2)	- 0.05 (-0.65–0.68)	<0.001
avPAH-SDS	-1.01 (-1.61– -0.25)	0.72 (0.06–1.39)	<0.001
Peak LH/peak FSH	0.85 (0.39–1.63)	NA	

Results

Of the 98 girls, 57 (58 %) reported menarche after completing GnRHa treatment. Among these 57 girls, median interval between end of treatment and onset of the menarche was 13.4 months (IQR, 9.4–18.5), and the mean age was 12.4 years (IQR, 11.1–14.2).

Univariate analysis indicated that five variables were predictive factors associated with the time to menarche: BMI SDS at start of treatment (HR, 1.33; 95% CI, 1.003–1.77), LH/FSH ratio at start of treatment (HR, 1.34; 95% CI, 1.04–1.72), and BMI SDS at end of treatment (HR, 1.88; SDS out of four highly cor95% CI, 1.34–2.64) (table 2). Of these five variables, multivariate model included BMI SDS at the end of therapy and LH/FSH ratio at start of therapy. To avoid multicollinearity, we selected only BMI related variables (i.e., weight SDS at start of therapy, BMI SDS at start of therapy, and weight SDS at end of therapy, and BMI SDS at end of therapy): BMI SDS at the end of therapy had the highest HR among these 4 predictors (Table 2).

Table 2. Univariate analyses of associated factors for the time to menarche

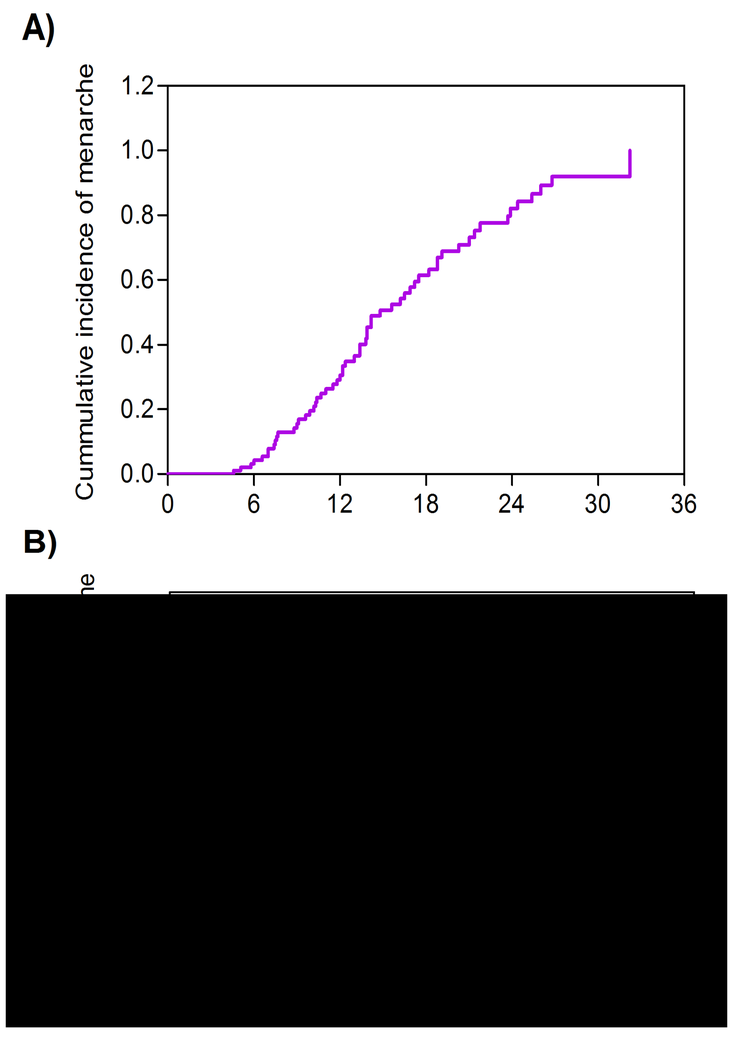
Variable	*P* value	HR (95% CI)
Parameters at start of therapy		
Age, years	0.46	0.90 (0.68–1.19)
CPP (compared to EP)	0.94	1.02 (0.56–1.88)
Midparental height, cm	0.63	0.98 (0.90–1.07)
Height SDS	0.07	1.36 (0.97-1.90)
Weight SDS, kg	0.017	1.49 (1.08–2.07)
BMI SDS	0.047	1.33 (1.00–1.77)
Bone age, years	0.47	1.10 (0.85–1.43)
Peak LH/peak FSH ratio	0.02	1.34 (1.04–1.72)
Treatment-related factors		
Duration of therapy, month	0.20	1.02 (0.99–1.04)
Cumulative dosage, μg/kg	0.82	1.04 (0.73–1.49)
Leuprilin (compared to decaptyl)	0.74	1.10 (0.63–1.93)
Parameters at end of therapy		
Age, years	0.32	1.29 (0.78–2.15)
Height SDS	0.30	1.22 (0.84–1.77)
Weight SDS	0.001	1.75 (1.26–2.42)
BMI SDS	<0.001	1.88 (1.34–2.64)
Bone age, years	0.10	1.43 (0.93–2.19)

Results

Multivariate analysis indicated only one risk predictive factors for time to menarche was BMI SDS at end of treatment (HR, 1.56; 95% CI, 1.06–2.29).

Kaplan-Meier plot showing the cumulative probability of onset of menarche among patients with CPP or EP who were treated with GnRHa is displayed in Figure 1A. Cumulative probability of incidence of onset of menarche was 31% at 12 months, 51% at 15 months, 61% at 18 months, and 82% at 24 months after completing treatment. To evaluate the association between BMI SDS at end of therapy and time to menarche, we categorized patients into two groups using the median BMI SDS of 0.78 at end of therapy. Time to menarche were shorter in patients with BMI SDS at end of therapy of ≥0.78 than in those with BMI SDS at end of therapy of <0.78 (log-rank test, P <0.001) (Figure 1B).

Figure 1. Kaplan-Meier plot showing time to menarche among patients with CPP or EP.



Conclusion

We found that onset of menarche was associated with BMI SDS at end of treatment.

These results suggest that hormonal and auxological parameters at start as well as at end of treatment are related to time of menarche.