Original Report

Comparison of the Clinical and Anthropometric Features of Treated and Untreated Girls with Borderline Early Puberty

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A B S T R A C T

Study Objective: Risks associated with precocious puberty might be observed in the rapidly progressive form of borderline early puberty (BEP). Differentiating the rate of progression is important for deciding treatment with gonadotropin-releasing hormone analogue (GnRHa). The aim was to examine the treatment characteristics and effect of treatment on predicted adult height (PAH).
Design: Retrospective observational study.
Setting: Single-center, a pediatric endocrinology unit.
Participants: A total of 135 girls, pubertal findings starting between 7-10 years of age.
Interventions: Data were collected via chart review. Patient groups were defined as treated with GnRHa (n = 63) or untreated (n = 72) girls.
Main Outcome Measures: Referral characteristics and anthropometric and pubertal findings of the patients with BEP, effect of treatment on PAH, and final height of the groups were compared.
Results: The mean (±SD) age of the patients at admission and for the first appearence of pubertal findings was 8.8 ± 1.0 and 8.0 ± 0.8 years, respectively. Target height and PAH-target height values at admission were similar. At initiation of treatment, PAH of the treated girls (157.8 ± 7.2 cm) were significantly lower compared with untreated girls (160.7 ± 6.5 cm). The age at menarche of patients in the treated and untreated groups were 12.3 ± 1.0 and 11.3 ± 1.1 years, respectively. The final height of the groups were similar (157.1 ± 6.6 vs 157.0 ± 5.9 cm; $P = .922$) despite a lower PAH of the treated group.
Conclusion: GnRHa treatment resulted in an increase in PAH and normalized the age of menarche in patients with BEP. In selected girls with rapidly progressive BEP, GnRHa treatment may be considered.
Key Words: Borderline early puberty, GnRH analogue, Precocious puberty

Introduction

Puberty represents a complex biological process of sexual development and children attain secondary sexual characteristics and reproductive capacity during this period. Genetic, nutritional, environmental, and socioeconomic factors might affect the onset and tempo of puberty although timing of puberty varies greatly.

Puberty starts in girls with the first appearance of breast buds and acceleration in growth velocity is also one of the earliest manifestation of puberty.[1,2] Central precocious puberty (CPP) is defined as the activation of the hypothalamo-pituitary-gonadotropic (HPG) axis before 8 years of age in girls. In a longitudinal study on pubertal status of girls, 8 years of age is still acceptable for the definition of precocious puberty.[3] The onset of pubertal findings after 8 years of age can be regarded as normal puberty, because it is statistically in the normal range. However, one of the most frequent variants of the CPP spectrum is the onset of puberty beginning with a normal but slightly earlier shift. On the basis of the normal distribution of age of onset of puberty, a significant proportion of children were included in the group "early puberty" (EP) or "borderline EP" (BEP). There is no agreed age range for BEP and consensus reports also differ.[4] The age range for BEP was agreed as 8-10 years[5,6]; 7.5-8.5 years,[7] 8-9 years,[8] or even as early as 6-8 years in different studies.[9] The CPP spectrum also includes "slowly progressive precocious puberty"[10] and "rapidly progressive precocious puberty." In its rapidly progressive form, BEP can be associated with problems more usually encountered in cases of precocious puberty such as compromised final height (FH).[11] Differentiating slowly progressive puberty from rapidly progressive puberty is important in terms of treatment decision.

Girls with pubertal findings starting before 6 years of age benefit most from gonadotropin-releasing hormone analogue (GnRHa) treatment. However, response to treatment might change in girls between 6-8 years of age.[12] In this age group, children with rapidly progressive puberty might benefit from treatment whereas slowly progressive ones might reach target height (TH) without treatment.[13] There is a limited number of studies about the treatment of BEP cases between 8-10 years of age[14,15] and it has been reported that GnRHa treatment had no effect on FH.[7] In the consensus report published in 2009, it was stated that the decision to start GnRHa after 6 years old should be

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evaluated on a patient by patient basis.[12] Although BEP should not necessarily be regarded as a serious condition, it might cause concerns in parents and also in practitioners, in terms of growth and psychological well-being of affected girls, raising the question to treat or not.[4,16,17]

In this study our aim was: (1) to examine the anthropometric measurements and hormonal values of the girls aged 7-10 years who presented with pubertal signs; (2) to compare the referral characteristics and anthropometric and pubertal findings of the treated and untreated patient groups; (3) to examine the treatment characteristics and effect of treatment on predicted adult height (PAH); and (4) to compare the FH of the treated and untreated groups.

Materials and Methods

Subjects

The study group included 135 girls with the diagnosis of BEP followed in the Pediatric Endocrinology Unit of Istanbul University Hospital.

The girls with pubertal findings starting between 7 and 10 years of age and had the diagnosis of BEP were included in the study. The study cohort was divided into subgroups. Group I (63 girls) consisted of patients treated with GnRHa for rapidly progressive puberty and group II (72 girls) included the untreated patients with slowly progressive puberty. Criteria used for the diagnosis of rapidly progressive puberty were bone age (BA) advancement greater than or equal to 1 year more than chronological age (CA) during any 4- to 6-month follow-up interval and PAH to be lower than TH.[18]

Patients with organic lesions on cranial and pituitary magnetic resonance imaging and those with central nervous system problems such as cerebral palsy or hydrocephalus were excluded. Patients with the diagnosis of growth hormone deficiency, uncontrolled thyroid disease, and adrenal or gonadal disorders expected to affect growth and puberty were not included in the study. Patients with skeletal dysplasia, genetically diagnosed dysmorphism, and those with a history of chronic use of medications known to cause EP were also excluded.

Inclusion and exclusion criteria for the study are summarized in Table 1.

Table 1
Inclusion and Exclusion Criteria of the Study

Inclusion Criteria	Exclusion Criteria
Girls whose pubertal findings started between 7-10 years of age	Pubertal findings starting before 7 years or after 10 years of age
Diagnosis of idiopathic central puberty according to clinical and hormonal evaluation	Gonadotropin-independent precocious puberty
Normal cranial and pituitary MRI	Organic lesion on cranial or pituitary MRI or genetic diagnosis or chronic drug use known to cause CPP
Bone age ≥14 years at last examination	Bone age <14 years at last examination
Patients with premature pubarche at admission in whom CAH was ruled out.	GH deficiency and CAH that can affect FH

CAH, congenital adrenal hyperplasia; CPP, central precocious puberty; FH, final height; GH, growth hormone; MRI, magnetic resonance imaging.

Patient Records and Data Collection

First Evaluation (Admission)

Complaints and age of the first appearence of pubertal findings were recorded. Pubertal stages according to Tanner classification, presence of central nervous system complaints or findings, pathologic features on physical examination (cafe-au-lait spots, bone deformities, acne, etc), which might be helpful for the differential diagnosis of EP were obtained from the patient records.

Information about birth status (gestational age, birth weight and length) were recorded. Prematurity was defined as gestational age less than 37 weeks. Birth weight was expressed as standard deviation score (SDS) according to gestational age.[19] Children were classified as small for gestational age (SGA) if birth weight and/or birth length SDS were less than −2.0 SDS.

Mother's age at menarche and any history of short stature and EP in the family were recorded from the medical files.

Anthropometric Measurements

Height and weight were measured in all subjects and their parents using a wall-mounted calibrated Harpenden Stadiometer (Holtain Ltd, Crymych, United Kingdom) and electronic scale sensitive to 0.1 kg. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. All measurements were expressed as SDS according to national standards.[20,21] Patients were categorized according to World Health Organization criteria according to BMI SDS. Cases with BMI SDS greater than or equal to 2 SDS were considered obese and those with BMI SDS between 1 and less than 2 SDS were considered as overweight. BA was assessed by a single observer using the Greulich and Pyle method. PAH on the basis of BA was calculated using the Bayley–Pinneau method. The patients with BA of 14 years or older were considered as having reached FH.[22]

Laboratory Investigations

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), 17 hydroxyprogesterone, prolactin, free thyroxine, and thyroid-stimulating hormone levels were evaluated using a morning blood sample in all cases. A basal serum LH greater than or equal to 0.3 mIU/L (with clinical findings) was accepted as activation of the HPG axis.[23] Standard stimulation test of 100 μg gonadotropin releasing hormone (GnRH) (Gonadorelin Acetate, LH-FSH 0.1 mg/mL; Ferring, Istanbul, Turkey) was performed with an intravenous injection between 8:00 and 8:30 AM to asses the patient for EP and blood samples were obtained at 0, 30, 60, and 90 minutes to measure serum LH and FSH levels. Peak LH greater than or equal to 5.0 mIU/L was accepted as activation of the HPG axis.[23]

Assays

LH and FSH values were analyzed using electrochemiluminiscense immunoassay (ECLIA; Modular Analytic E170; Roche Diagnostic, Istanbul, Turkey). Intra-assay coefficient of variation (CV) for LH and FSH were 0.6%-1.2% and

1.3%-2.8%, respectively. Interassay CV for LH and FSH were 1.6%-2.2% and 3.6%-4.5%, respectively. The lowest LH and FSH levels that can be determined using this method are 0.1 mIU/L. E2 levels were measured using ECLIA (Modular Analytic E170; Roche Diagnostic). Intra-assay CV was 1.4%-3.3% and interassay CV 2.2%-4.7% for E2. The lower limit of detecion for E2 was 5.0 pg/mL. The 17 hydroxyprogesterone level was measured using an Immunotech17 OH progesterone radioimmunoassay (Diagnostic Systems Laboratories, Inc, TX). Intra-assay CV was 3.1%-7.55% and interassay CV was 5.52%-12.87% for 17 hydroxyprogesterone. Free thyroxine and thyroid-stimulating hormone levels were measured using ECLIA (Modular Analytic E170; Roche Diagnostic). Intra-assay CV was 1.4%-2% and 1.2%-3.0%, respectively. Interassay CV was 2.6%-4.8% and 3.2%-7.2%, respectively.

Radiology

Pelvic ultrasonography (US) was performed at the time of diagnosis in all cases to evaluate the consistency of pubertal findings with the US findings. Transabdominal pelvic US was performed by 1 experienced pediatric radiologist using Logiq 9 (GE Healthcare, Milwaukee, WI) using the device's 12-MHz probe. Uterus length greater than 3.5 cm and ovarian volume greater than 1.5 cm^3 were accepted as criteria for supporting EP.[24] Pelvic US findings were evaluated in conjunction with the other clinical and laboratory parameters mentioned previously.

Cranial and pituitary magnetic resonance imaging was performed to rule out an organic lesion in cases between 7 and 8 years of age. Cases with organic lesions were excluded from the study.

Evaluation During Follow-up

The patients were evaluated at 4- to 6-month intervals during follow-up. Pubertal stages, height, weight, BMI SDS, PAH SDS, height velocity, and BA of all of the patients in the study were recorded. Date of menarche was also recorded.

Evaluation of the Patients during GnRHa Treatment

GnRHa treatment was initiated in those with BA advancement of 1 year or more compared with CA during the 4- to 6-month follow-up after admission and PAH less than TH. The date of treatment initiation and the name and dose of the drug, date of the termination of treatment, and age of the patient were recorded. Changes in the treatment dose and side effects during treatment were also recorded.

Statistical Analyses

Analyses were performed using the Statistical Package for the Social Sciences version 22.0 program (IBM Corp, Armonk, NY). Differences between groups and parametric data were compared using Student *t* test. For the comparison of nonparametric data, the Mann–Whitney *U* test was used. Intragroup comparisons were done using the paired *t* test for parametric and Wilcoxon rank test for the nonparametric data. The relationship between the data were analyzed using Pearson correlation (correlation coefficient: *r*) for parametric and Spearman correlation (correlation coefficient: *rs*) for the nonparametric data. A *P* value of .05 or less was considered statistically significant.

The study was approved by the local ethics committee (2016/58).

Results

Clinical, Laboratory, and Radiologic Features of Patients at First Evaluation (Admission)

The study included 135 girls with the diagnosis of EP. Mean (±SD) age of the patients at admission was 8.8 (±1.0) years and mean (±SD) age for the first appearence of pubertal findings was 8.0 (±0.8) years (range, 6.8-9.7 years). Mean time interval for admission after appearence of pubertal findings was 9.1 months.

Physical examination and presenting complaints of the girls revealed breast and pubic hair present in 35 girls (25.9 %); breast development only in 31 girls (23%); and breast, pubic, and axillary hair in 56 girls (41.5%). In 10 cases (7.4%) puberty started with pubarche. Fifteen girls (11.1%) had a history of menarche at admission. The mean (±SD) age of the patients with menarche was 9.4 (±1.0) years (range, 7.3-11.0 years).

In the cohort, 18.5% (n = 25) of the patients were SGA, 5.2% (n = 7) were large for gestational age and 12.6% (n = 17) were premature newborns. The mean (±SD) of the mother's age at menarche was 12.5 (±1.3) years (range, 8-16 years) and in 28 cases with older sisters the mean for the sister's age at menarche was 12.3 (±0.8) years (range, 11-14 years).

Familial history of precocious or EP was 8.8%. Of the 135 girls evaluated, 11 (8.1%) were obese and 49 (36.3%) were overweight. None of the SGA girls were obese at admission, however, overweight ratio was 28%. In the appropriate for gestational age (AGA) group, obesity and overweight ratio were 10.7% and 37.9%, respectively. BMI SDS of the SGA and AGA subjects at admission were similar (0.5 ± 0.9 vs 0.9 ± 1.1, respectively; $P = .153$).

Comparison of the Data of Group I and Group II at Admission

At admission, the mean age of the patients in group I (8.5 ± 0.9 years) was significantly younger than group II (9.0 ± 1.0 years; $P = .002$). There was also a significant difference between group I and group II for the age of onset of pubertal findings and time interval for the admission. Mother's age at menarche was significantly younger in group I (12.1 ± 1.3 years) compared with group II (12.8 ± 1.2 years; $P = .001$).

At admission, height, weight, and BMI SDS of the patients in the 2 groups were not different. In addition TH SDS and PAH-TH SDS values at first evaluation were not statistically different. PAH and PAH SDS of group I (157.8 ± 7.2 cm and −1.0 ± 1.2) was significantly lower compared with group II (160.7 ± 6.5 cm and −0.5 ± 1.1) with *P* values for PAH and PAH SDS of .017 and .015, respectively. According to Tanner staging, breast stage was more advanced in group I

compared with group II whereas no significant difference was detected between the groups for pubic and axillary hair. Basal LH, basal FSH, E2, and peak LH and peak LH/peak FSH after GnRH stimulation test were significantly higher in group I than group II. Pelvic US was performed at admission and there was not a significant difference between the largest size of the uterus and ovarian volume.

A comparison of the demographic, anthropometric, laboratory, and radiologic characteristics of group I and group II at admission are summarized in Table 2.

Characteristics of the Patients at Initiation of GnRHa Treatment

In 23 of 135 patients, GnRHa treatment was started at the first evaluation. The reason to start treatment were: (1) peak LH level was pubertal in the GnRH stimulation test and BA of greater than or equal to 2 SDS more than CA; (2) basal LH was too high and BA of greater than or equal to 2 SDS more than CA; and (3) menarche and (4) puberty stages were higher than Tanner III-IV and BA greater than or equal to 2 SDS more than CA.

It was decided to start GnRHa treatment at follow-up after 4-6 months, in an additional 40 patients. The reason for the initiation of treatment in most of these patients were the rapid advancement of BA, PAH to be lower than TH, and rapid progression of the puberty. Treatment was started about an average of 7.3 (±8.9; range, 0-34) months after admission. Mean age for the initiation of treatment was 9.1 (±0.9; range, 7.4-11.5) years, and mean age at the termination of treatment was 11.4 (±0.9; range, 10-14.3) years. Mean interval for the treatment was 2.2 (±0.8; range, 0.7-4.5) years.

Comparison of the Anthropometric Measurements and Laboratory Data of Group I and II at Treatment İnitiation Time

The comparison of the anthropometric measurements and the laboratory data of group I and group II at initiation of therapy are summarized in Table 3. Mean values of anthropometric measurements and laboratory data of group II at 7.2 (±2.8) months of follow-up were used for comparison of the groups. Pelvic US was performed in 6 patients and peak LH and FSH values on GnRH stimulation test were present in 4 patients in group II; therefore, these parameters were excluded from analyses. BA was advanced in group I compared with group II. PAH and PAH SDS were significantly lower in group I compared with group II and the difference was more prominent at the time of treatment initiation. Although PAH SDS-TH SDS was not different between the groups at admission, it was significantly different at the start of treatment. Basal LH was significantly higher in group I, at admission and at the start of treatment. E2 was significantly higher in group I at admission but there was no difference between the groups at treatment initiation.

A comparison of the follow-up data of both groups are illustrated in Figure 1.

Table 2
Comparison of the Demographic, Anthropometric, Laboratory and Radiologic Features of the Patients in Group I and Group II at Admission

Features of the Patients	Group I (n = 63)	Group II (n = 72)	*P*
Age at admission, years	8.5 ± 0.9	9.0 ± 1.0	**.002**
First appearence of symptoms, years	7.9 ± 0.8	8.2 ± 0.7	**.041**
Duration of symptoms, months	7.4 ± 6.4	10.5 ± 8.7	**.022**
SGA	12 (19.0%)	13 (18.1%)	.841
Prematurity	9 (14.3%)	8 (11.1%)	.808
Mother's age at menarche, years	12.1 ± 1.3	12.8 ± 1.2	**.001**
Height SDS	0.65 ± 1.33	0.5 ± 1.2	.551
Weight SDS	0.9 ± 1.2	0.8 ± 1.1	.654
BMI SDS	0.8 ± 1.1	0.8 ± 1.0	.846
TH SDS	−1.1 ± 0.9	−0.9 ± 0.8	.150
Bone age, years	10.1 ± 1.5 (n = 60)	9.9 ± 2.0 (n = 68)	.564
PAH SDS	−1.0 ± 1.2	−0.5 ± 1.1	**.015**
PAH SDS-TH SDS	0.10 ± 1.1	0.43 ± 1.0	.081
Bone age/chronological age	1.2 ± 0.15	1.1 ± 0.1	<**.001**

BMI, body mass index; SGA, small for gestational age; SDS, standard deviation score; TH, target height; PAH, predicted adult height.
Data are presented as n (%) or mean ± SD, except where otherwise noted.
Statistically significant *P* values are shown in bold.

Table 3
Comparison of the Anthropometric Measurements and Laboratory Data of Group I at the Time of Treatment Initiation and Group II After 4-6 Months of Follow-up

Variable	Group I	Group II	*P*
Age, years	9.1 ± 0.9	9.6 ± 1.0	**.007**
Time interval after admission, months	7.3 ± 8.9	7.20 ± 2.8	.912
Height SDS	0.9 ± 1.3	0.6 ± 1.1	.240
Weight SDS	1.0 ± 1.2	0.9 ± 1.0	.480
BMI SDS	0.8 ± 1.1	0.8 ± 1.0	.840
Bone age (years)	11.1 ± 1.1 (n = 58)	10.3 ± 1.8 (n = 52)	**.003**
ΔBA/ΔCA	2.0 ± 1.3	1.1 ± 1.3	**.003**
PAH SDS	−1.1 ± 1.3	−0.4 ± 1.0 (n = 67)	**.002**
PAH SDS-TH SDS	−0.0 ± 1.1	0.5 ± 1.0	**.025**
Pubertal stage			
Breast	2.9 ± 0.7	2.6 ± 0.9	**.026**
Pubic	2.4 ± 1.0	2.5 ± 0.9	.719
LH, mIU/mL	2.3 ± 2.3 (n = 43)	1.1 ± 1.55 (n = 20)	**.038**
FSH, mIU/mL	4.1 ± 2.1 (n = 43)	3.7 ± 2.7 (n = 20)	.496
E2, pg/mL	39.3 ± 32 (n = 43)	33.5 ± 40.1 (n = 20)	.550

BA, bone age; CA, chronological age; BMI, body mass index; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PAH, predicted adult height; SDS, standard deviation score; TH, target height.
For group I n = 63 and for group II n = 67 except where otherwise noted.
Statistically significant *P* values are shown in bold.

Comparison of the TH and FH of Group I and Group II

At admission, TH and TH SDS of the 2 groups were not different. FH and FH SDS of group I and group II were not statistically different. Neither did FH-TH and FH SDS-TH SDS of group I and group II differ. TH SDS and FH SDS of group I and group II are summarized in Table 4.

Group I was also analyzed in 2 subgroups: comparison of the FH of 23 patients that started GnRHa treatment at first evaluation were compared with the other 40 patients who started treatment at follow-up. There was no significant difference between the FH (156.1 ± 4.5 cm vs 157.4 ± 7.8 cm; $P = .393$) and FH-TH difference (−0.5 ± 4.5 vs 0.4 ± 6.4 cm; $P = .507$) of these 2 subgroups.

Comparisons of the PAH during follow-up and FH and TH of the groups are illustrated in Figure 2. It is noteworthy that PAH decreased in group I before treatment, normalized after treatment, and became similar to that of group II.

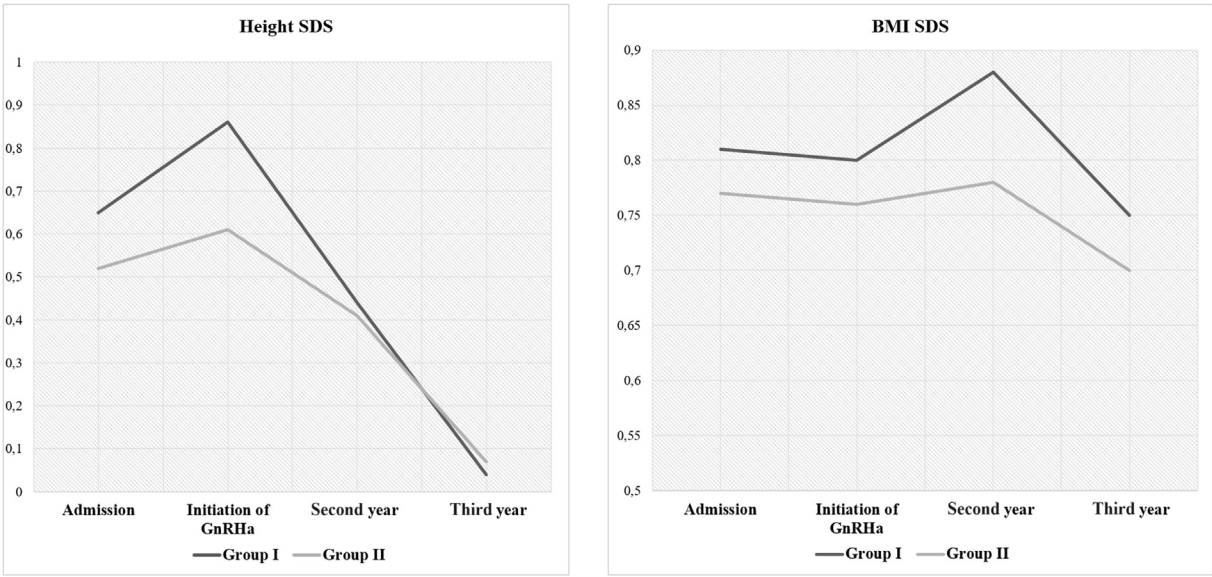

Fig. 1. Change in height SDS and BMI SDS during follow-up. BMI, body mass index; SDS, standard deviation score.

In the SGA group, there was no correlation between BMI SDS at admission and FH-TH difference.

Menarcheal Status of the Groups

In the whole group mean (±SD) age at menarche was 11.8 (±1.2; range, 8.6-14.8) years. Age at menarche of patients in group I and group II were 12.3 (±1.0; range, 8.6-14.7) and 11.3 (±1.1; range, 9.1-14.6) years, respectively. It is noteworthy that age at menarche of group I was significantly more advanced than in group II. The menarcheal age of the untreated girls was earlier than that in the normal population. In group I, patients had menarche at an average of 10.6 (±7.8) months after cessation of GnRHa.

In the untreated group, the mean (±SD) age at menarche of SGA and non-SGA girls was 11.2 (±1.1) and 11.3 (±1.1) years, respectively, which was not significantly different ($P = .67$).

Discussion

BEP has 2 tempos, either the slowly or rapidly progressing form. Rapid progression of puberty might lead to accelerated growth and bone maturation resulting in a decrease in FH. However, uncertainty exists on the efficacy of GnRHa treatment in girls with BEP.[11,17]

In our study, we treated girls with rapidly progressing BEP and compared their results with that of slowly progressing, untreated BEP. It is noteworthy that the decreasing PAH in the rapidly progressing group normalized during GnRHa treatment and menarcheal age was within the population norm and at an older age than that of their mothers. The untreated girls, however, had an earlier menarche than those who were treated. FH did not differ between the groups. However we speculate that the decrease in PAH over the years in the rapidly progressive BEP group might be indicative of a compromised FH. So GnRHa therapy in these girls resulted in a height similar to that for the untreated girls.

Table 4
Comparison of the TH, FH, and FH SDS-TH SDS of Group I and Group II

Variable	Group I (n = 63)	Group II (n = 72)	*P*
TH, cm	156.9 ± 5.4	158.2 ± 4.7	.147
TH SDS	−1.1 ± 0.9	−0.9 ± 0.8	.150
FH, cm	157.1 ± 6.6	157.0 ± 5.9	.922
FH SDS	−1.1 ± 1.1	−1.1 ± 1.0	.923
FH − TH, cm	0.2 ± 5.6	−1.21 ± 4.6	.123
FH SDS − TH SDS	0.1 ± 1.0	−0.2 ± 0.8	.131

FH, final height; SDS, standard deviation score; TH, target height.
Values are (Mean ± SD) except where otherwise noted.

Initial studies with GnRHa have reported significant improvement in FH during treatment in patients with CPP.[25] However, there are few studies on the results of GnRHa treatment in patients with BEP compared with the results of untreated girls. In the study of Bouvattier et al,[6] the authors compared the results of FH of a group with EP which was similar to that of untreated girls in our study. Although GnRHa delayed sexual maturation, growth rate, and BA, they had no clear-cut longstanding effect, and FH was comparable in treated and untreated girls.

In subsequent studies it has been reported that GnRHa treatment had no positive effect on FH in BEP or physiological normal puberty with rapid progression.[14,15] Thus it can be concluded that BEP within normal physiological range has a small (2-4 cm) effect on FH, an observation consistent with none to very small height gain achieved with GnRHa treatment of girls with BEP.[7,26,27] Estimation of the height loss caused by BEP is difficult to predict because the data in these subjects are scarce and methodologies in relevant studies is inconsistent.

We compared the results of GnRHa therapy in girls with rapidly progressive BEP with that of girls with nonprogressive/slowly progressive BEP. It would have been better to have included girls with untreated, rapidly progressive EP as a control group in this type of study. However, in clinical practice patients with advanced BA, increase in somatic growth, and progression of pubertal findings are

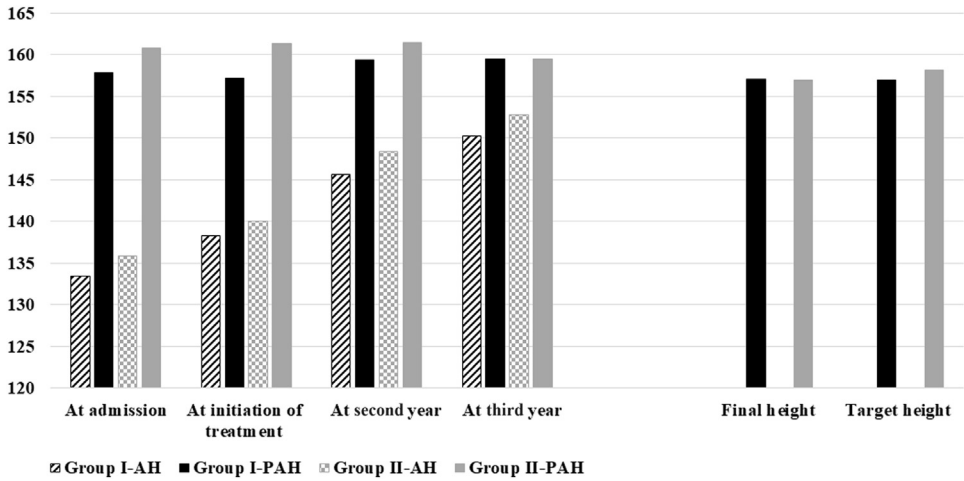

Fig. 2. Comparison of actual height (AH) and predicted adult height (PAH) during follow-up, final height, and target height. Black bars indicate group I and gray bars indicate group II.

treated most frequently. Patients whose parents refuse treatment might be a suitable control group to compare FH of the treated and untreated girls with BEP.

The mean age for the mother's age of menarche was 12.5 (±1.3) years and the results were similar to previous studies in our population.[3] However, it is noteworthy that the menarcheal age of the untreated BEP girls was younger than the normal population, even in the presence of slow puberty. Conversely, girls with rapidly progressive puberty normalized their menarcheal age with GnRHa treatment.

The onset of puberty in girls is highly sensitive to nutritional status and obesity might lead to premature thelarche or EP during childhood.[28–30] In a large, population-based, cross-sectional study the total ratio of precocious puberty was 9.5%. In this Chinese study, 13.9% of girls with precocious puberty had obesity and it was concluded that obesity increased the risk of precocious puberty.[31] In our study girls with BEP were not prominently obese compared with population norms and BMI SDS of the 2 groups were similar at admission and also BMI SDS of SGA and AGA girls were similar.

The onset of puberty and age of menarche might be earlier in SGA girls as reported in previous studies.[32] In our study the ratio of SGA was 18.5% and there was not a difference between the groups. In a prospective study, it was reported that SGA girls had a significantly earlier age of menarche than AGA and large for gestational age girls.[33] The age of menarche of the untreated SGA and non-SGA girls were not different in our cohort. In another study that compared SGA and controls, SGA girls had significantly lower mean FH than the controls and it was concluded that term-born SGA girls had impaired FH but normal age at menarche.[34] A higher proportion of SGA birth was detected, compared with the normal population frequency, in our study. Although this supports the idea that SGA might be a risk factor for EP, the numbers are not sufficient to draw any robust conclusions.

The effects of GnRHa treatment on BMI is controversial in girls with CPP. In CPP, patients have a higher obesity likelihood compared with the normal population. GnRHa treatment might have different effects according to baseline body composition.[35] Some studies have reported an association between GnRHa treatment and increased BMI[36–38] whereas others have described no association[39] or even an association with decreased BMI during treatment.[40,41] Yang et al reported that the proportion of overweight/obesity was high in girls with CPP,[42] however, in the whole group no significant change in BMI was observed during the GnRHa treatment. Baseline BMI was described as an independent predictor of BMI changes during treatment. In our study, BMI SDS values during follow-up in the treated and untreated girls were not significantly different. Thus, the high rates of overweight and obese cases might be linked to an overall increase in obesity prevalence in Turkish children, rather than GnRHa treatment. Nevertheless, it is important to investigate the GnRHa effect on BMI in children with precocious puberty, because of increasing childhood obesity worldwide.

BA and PAH are important parameters in following EP cases and treatment is not indicated if pubertal progress is slow. However, patients with advanced BA and decrease in PAH should be evaluated to make a treatment decision. Considering the cost is also another important issue in treatment decision. In our study, all of the patients with the rapidly progressive form of EP were treated. We do not know what would have happenned if we had not treated them but the decrease in PAH normalized during treatment and the girls had menarche at an age appropriate for our normal population. The untreated girls had an earlier menarche. Prospective studies only on girls with rapidly progressing BEP to assess the effect of GnRHa on FH are required. In conclusion, in selected girls with rapidly progressive BEP, GnRHa treatment should be considered.

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