ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Retrospective Evaluation of Patients Presenting with Puberty Precocious Complaints with Clinical and Laboratory Findings

Puberte Prekoks Şikayetleri ile Başvuran Hastaların Klinik ve Laboratuvar Bulguları ile Retrospektif Olarak Değerlendirilmesi

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Abstract

Introduction: In this study, clinical characteristics and laboratory results of girls presenting with precocious puberty complaints were compared according to age groups. The effects of GnRHa (gonadotropin-releasing hormone analog) treatment were evaluated by assessing the anthropometric data and predicted adult height (PAH) of the treated and untreated cases.

Materials and Methods: A total of 75 girls were included in the study. Cases were divided into four groups; cases between the ages of 5-8 years who started treatment constituted Group 1 and those who did not start treatment constituted Group 2; cases between the ages of 8-10 years who started treatment constituted Group 3 and those who did not start treatment constituted Group 4. The anthropometric data, pubertal stages, bone age (BA), the change in the ratio of BA to chronological age (CA) (BA/CA), and the changes in PAH during follow-up were analyzed.

Results: Target Height (TH) - PAH changes were compared in the treated and untreated groups. C Height, height-SDS, BMI, BMI-SDS, PAH, TH, TH-PAH values, and pubertal developmental stages at presentation were similar between Group 1 and Group 2, and between Group 3 and Group 4. At the initial presentation, the BA and BA/CA values of Group 1 and Group 2 were similar, whereas the BA value in Group 3 was significantly more advanced than in Group 4. BA/CA values at presentation were similar between groups 3 and 4. During follow-up, height, height-SDS, BMI, BMI-SDS, BA, and BA/CA changes were similar, and TH - PAH values were similar in the treated and untreated groups.

Conclusion: According to age groups, ΔBA/ΔCA, TH – PAH, ΔBMI-SDS values were similar between treated and untreated subjects, and GnRHa treatment had no significant effect on height and weight during follow-up in our case group.

Keywords
Precoccious puberty, GnRHa therapy, predicted adult height

Anahtar kelimeler
Puberte prekoks, GnRHa tedavisi, öngörülen son boy

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Öz

Giriş: Bu çalışmada puberte prekoks şikayetleri ile başvuran kız çocuklarının klinik özellikleri ve laboratuvar sonuçları yaş gruplarına göre karşılaştırıldı. GnRHa (gonadotropin salgılatıcı hormon analoğu) tedavisinin etkileri, tedavi edilen ve edilmeyen olguların antropometrik verileri ve öngörülen son boyları (ÖSB) hesaplanarak değerlendirildi.

Gereç ve Yöntem: Çalışmaya toplam 75 kız çocuğu dahil edildi. Olgular dört gruba ayrıldı; 5-8 yaş arasında tedavi başlananlar Grup 1'i, başlanmayanlar Grup 2'yi; 8-10 yaş arasında tedavi başlananlar Grup 3'ü, başlanmayanlar Grup 4'ü oluşturdu. Antropometrik veriler, puberte evreleri, kemik yaşı (KY), KY'nın takvim yaşına (TY)

oranındaki değişim (KY/TY) ve takip sırasında ÖSB'deki değişiklikler analiz edildi. Hedef Boy (HB) - ÖSB değişiklikleri tedavi edilen ve edilmeyen gruplarda karşılaştırıldı.
Bulgular: Başvuru sırasındaki boy, boy-SDS, VKI, VKI-SDS, ÖSB, HB, HB - ÖSB değerleri ve pubertal gelişim evreleri Grup 1 ve Grup 2 ile Grup 3 ve Grup 4 arasında benzerdi. İlk başvuru sırasında Grup 1 ve Grup 2'nin KY ve KY/TY değerleri benzerken, Grup 3'ün KY değeri Grup 4'e göre anlamlı derecede daha ileriydi. Başvuru sırasındaki KY/TY değerleri Grup 3 ve 4 arasında benzerdi. Takip sırasında boy, boy-SDS, VKI, VKI-SDS, KY ve KY/TY değişiklikleri benzerdi ve HB - ÖSB değerleri tedavi edilen ve edilmeyen gruplarda benzerdi.
Sonuç: Yaş gruplarına göre, ΔKY/ΔTY, HB - ÖSB, ΔVKI-SDS değerleri tedavi edilen ve edilmeyen olgular arasında benzerdi ve GnRHa tedavisinin olgu grubumuzda takip sırasında boy ve kilo üzerinde anlamlı bir etkisi yoktu.

Introduction

The onset of breast development in girls before the age of 8 years is called precocious puberty (PP) (1). However, the age of onset and progression of puberty are heterogeneous (2-4). In an early completed pubertal development, a temporary tall stature first occurs due to the peak growth rate experienced in the early stages of puberty. However, due to the premature closure of the epiphyseal plates, the target height (TH) cannot be reached, and the final height (FH) becomes short. Therefore, early onset of puberty is associated with short stature (5,6). This situation leads to the concern that the final adult height will be short, which has been increasing worldwide, especially in the last 20 years. This results in an increase in unnecessary outpatient clinic visits (7).

In the treatment of PP, GnRHa (gonadotropin-releasing hormone agonists) are used that suppress the hypothalamic-pituitary-gonadal axis (HHG). This treatment is aimed to stop the progression of puberty and bone age (BA) so that the child can reach the target height (TH) (8). However, recently, it has also become widespread that GnRHa treatment does not increase final height (FH) as much as thought (9). It is not clear whether pubertal development, especially starting early and continuing within the normal range, causes short stature (2,3). Those with slowly progressing puberty or those close to the age of normal pubertal development can reach their predicted adult height (PAH) even without any treatment (9,10). It is reported that those who benefit most from treatment are children whose pubertal development begins at an early age, especially before the age of 6, and has a rapid course (1,9). For girls with later-onset central precocious puberty (CPP) and/or slowly progressing puberty without a growth spurt, it is recommended that pubertal progression be followed up at three to six-month intervals (3).

The need for a critical weight for growth spurt and menarche in adolescent girls was stated by Frish and Revelle about 55 years ago (11,12). In a study, a significant increase in BMI was reported in the transition from stage 1 to stage 2 of puberty (13) and early menarche was associated with high body mass index (BMI) (14). In addition, there are also papers indicating that GnRHa treatment increases obesity in patients (15).

In this study, we aimed to investigate the effect of treatment on height, weight, BMI, BA and PAH by grouping the patients according to their age and whether they received treatment or not. In addition, we aimed to investigate the prevalence of overweight/obesity in PP patients by determining the overweight/obesity ratio of the patients at the beginning of treatment.

Materials and Methods

Cases who presented to the pediatric endocrinology outpatient clinic of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital l between January 2015 and January 2017 with findings of breast development, pubic hair growth, axillary hair growth and menarche were assessed. The records of 75 girls who were followed up for at least 1 year were evaluated retrospectively. The patients were divided into groups according to their age and puberty-arresting treatment initiation status. Accordingly, Group 1 consisted of 28 patients aged 5-8 years who were started on medication; Group 2 consisted of 23 patients aged 5-8 years who were not started on medication; Group 3 consisted of 5 patients aged 8-10 years who were started on medication; and Group 4 consisted of 19 patients aged 8-10 years who were not started on medication.

At 3-month intervals, height and BMI were calculated at each visit and compared with the standard curves established for Turkish children, and height-SDS and BMI-SDS were calculated according to chronological ages (CA) (16). Subjects with a BMI-SDS value above 2 SDS were considered obese and subjects with a BMI-SDS value between 1.5 SDS and 2 SDS were considered overweight. Pubertal status was determined according to Tanner staging based on breast development and pubic hair growth (17). LH, FSH, and estradiol measurements were performed. Basal LH level ≥ 0.3 mIU/L was considered as activation of the HHG axis. In

GnRH stimulation test performed in patients with basal LH level <0.3 mIU/mL, LH ≥ 5mIU/mL or LH/FSH ratio >0.66 was considered as activation of the HHG axis. Pelvic USG was performed at initial presentation and at 6-month intervals. On pelvic USG, ovarian volumes >1-3 mL, uterine size >3.4-4 cm and volume >2-3mL and endometrial thickness >2-3 mL were considered as findings supporting precocious puberty.

Left wrist radiography was performed in all patients at admission and then once a year during follow-up and BA was determined according to the Greulich-Pyle atlas. According to BA, PAHs were calculated using the Bayley-Pinneau method. Bone maturation was calculated using the ΔBA/ΔCA ratio, taking into account the annual change in the treated and untreated groups. The heights of the parents were measured in the outpatient clinic and the target heights (TH) and TH-SDS of the patients were calculated. TH for girls was calculated with the formula (mother's height + father's height − 13) ÷ 2. THs were compared with PAHs according to years. The effect of treatment on height was evaluated by comparing the TH - PAH difference between the treated and untreated groups. Brain and pituitary MRI was performed to detect possible intracranial pathology in patients with pubertal symptoms that began before the age of six, and who had rapidly progressing pubertal symptoms.

Ethics committee approval was obtained from University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital on 17.07.2017 with protocol number 17.07.2017-2017/07/23.

Statistical Analysis

Data were analyzed with SPSS for Windows version 23.0. Descriptive statistics of continuous variables were expressed as mean and standard deviation; categorical variables were expressed as numbers and percentages. For categorical variables, the significance of the difference between the groups was evaluated by Chi-Square test. The significance of the difference between the continuous variables of the paired groups was evaluated by Mann Whitney-U test. A value of $P < 0.05$ was considered statistically significant.

Results

Of 75 patients, 36 (48%) were diagnosed with ICPP and 24 (66%) of these patients had rapidly progressive puberty. At the time of initial presentation, the mean age of Group 1 was 7 ± 0.8 years, and the mean age of Group 2 was 6.8 ± 0.8 years, and there was no significant difference between them (p: 0.407). The complaints of the patients in Group 1 started 5±4 months before the first visit, and those of the patients in Group 2 started 6±8 months before, and they were statistically similar (p:0.825). Of all patients, 10% were obese and 11% were overweight. Overweight or obese patients constituted 35.7% (10) of the patients in Group 1, 30.4% (7) of the patients in Group 2 and 21% (4) of the patients in Group 4. There were no overweight or obese patients in Group 3. Overweight/obese ratio was higher in Group 1 and Group 2. Brain and pituitary MRI was performed in 26% (20) of the patients and no pathology was found.

Table 1 shows the anthropometric data, pubertal stages, laboratory findings and BAs of all groups at the time of initial presentation. At baseline, there was no statistically significant difference between Groups 1 and 2 in terms of height, height-SDS, BMI, BMI-SDS values (124.5cm and 123cm, p_1: 0. 264; 0.7 and 0.6, p_2: 0.339; 17.7kg/m^2 and 17.8kg/m^2, p_3: 0.828; 0.9 and 1, p_4: 0.762). Breast development and pubarche stages were similar in Group 1 and Group 2 (p_1: 0.339, p_2: 0.510). There was no statistically significant difference between the FSH, LH and estradiol values of Group 1 and Group 2 at baseline (p_1: 0.092, p_2: 0.155, p_3: 0.154). The median values of BA and BA/CA at baseline were 7.8 years and 1.07 in Group 1 and 7.5 years and 1.01 in Group 2, respectively, and there was no statistically significant difference between them (p_1: 0.124; p_2: 0.059).

The mean age at initial presentation was 8.7 ± 0.3 years in Group 3 and 8.4 ± 0.3 years in Group 4 and there was no significant difference between them (p: 0.343). The complaints of the patients in Group 3 started 8 ± 4 months before the first visit, and those of the patients in Group 4 started 7 ± 4 months before, and they were statistically similar (p:0.743). At baseline, there was no significant difference between Groups 3 and 4 in terms of height, height-SDS, BMI, BMI-SDS values (130cm and 129.5cm, p_1: 0.498; 0.5 and -0.1, p_2: 0.320; 18.6 kg/m2 and 17.2 kg/m2, p_3: 0.374; 0.9 and 0.5, p_4: 0.414). Breast development stages were similar in Group 3 and Group 4 (p: 0.077), whereas the pubarche stage was more advanced in Group 4 (p: 0.038). There was no significant difference between groups 3 and 4 in terms of FSH, LH and estradiol median values at baseline (p_1: 0.402, p_2: 0.198, p_3: 0.099). The median value of BA at presentation was 9 years in Group 3 and 8 years in Group 4 and was significantly higher in Group 3 (p:0.043). The BA/CA median value was 0.98 in Group 3 and 0.97 in Group 4 and statistically similar (p:0.238) (Table 1, Figure 1).

Group 1 was followed-up for a mean of 2.4 ± 0.8 years and Group 2 for a mean of 1.9 ± 0.8 years and there was no difference between them in terms of follow-up time (p:0.063). The median height, height-SDS, BMI and BMI-SDS changes

in Group 1 and Group 2 were statistically similar during the follow-up period (12.2 cm and 9.5 cm, p_1: 0.140; 0.1 and 0.2, p_2: 0.501; 2.2 kg/m2 and 1.68 kg/m2, p_3: 0.399; 0.16 and 0.13, p_4: 0.520) (Table 2). There was no significant difference between groups 1 and 2 in pubertal stages at presentation, in the first year and in the second year (p_1:0.526; p_2:0.307, p_3:0.513). The median value of BA change was 2 years in Group 1 and 1.3 years in Group 2 and was statistically similar (p:0.231). At the first year of follow-up, the median value of ΔBA/ΔCA was 1.09 in Group 1 and 0.66 in Group 2 and there was no statistically significant difference between them (p:0.297). At the second year of follow-up, the median value of ΔBA/CA was 0.9 in Group 1 and 0.92 in Group 2, with no statistically significant difference (p:0.580) (Table 2).

The mean follow-up times of groups 3 and 4 were 1.6 ± 0.4 years and 1.5 ± 0.4 years, respectively, and statistically similar (p:0.894). The median height, height-SDS, BMI and BMI-SDS changes of Group 3 and Group 4 were statistically similar during the follow-up period (9cm and 9.5cm, p_1: 0.972; 0.03 and 0.2, p_2: 0.082; 2.9kg/m^2 and 1.3kg/m^2, p_3:

Table 1. Anthropometric data, pubertal stages, laboratory values and bone ages at baseline in all groups

	Group 1 median (min – max)	**Group 2 median (min – max)**	**p**	**Group 3 median (min – max)**	**Group 4 median (min – max)**	**P**
Age, year	7.1 (5 – 7.9)	7 (5.1 – 7.9)	0.718	8.7 (8.3 – 9.1)	8.4 (8 – 8.9)	0.068
Height, cm	124,5 (109.5 – 144.5)	123 (108.5 – 130.6)	0.264	130 (128 – 141)	129.5 (118 – 142)	0.498
Height-SDS	0,7 (-2.2 – 27)	0,6 (-2.2 – 2.5)	0.339	0.5 (-0.5 – 2.1)	-0.1 (-1.9 – 1.8)	0.320
BMI, kg/m^2	17,7 (13.8 – 23.7)	17,8 (13.2 – 23)	0.828	18.6 (15.9 – 19.9)	17.2 (13.8 – 24.5)	0.374
BMI-SDS	0,9 (-1.1 – 2.5)	1 (-1.7 – 2.5)	0.762	0.9 (-0.2 – 1.3)	0.5 (-1.5 – 2.3)	0.414
Thelarche n, (%) 1 2 3 4 5	 3 (11%) 14 (50%) 10 (36%) 1 (3%) -	 6 (26%) 12 (52%) 5 (22%) - -	0.339	 - 1 (20%) 4 (80%) - -	 6 (32%) 8 (42%) 5 (26%) - -	0.077
Pubarche n, (%) 1 2 3 4 5	 17 (61%) 11 (39%) - - -	 16 (70%) 7 (30%) - - -	0.510	 2 (40%) 1 (20%) 2 (40%) - -	 12 (63%) 7 (37%) - - -	0.038
FSH, mIU/L	3.47 (0.8 – 11.2)	1.89 (0.7 – 11.1)	0.092	3,95 (1,9 – 6,1)	2.,5 (0.6 – 6.4)	0.402
LH, mIU/L	0.38 (0.1 – 4.2)	0.25 (0 – 1.6)	0.155	2.08 (0.1 – 2.1)	0.45 (0.05 – 1.8)	0.198
Estradiol, pg/mL <20 ≥20	 15 (75%) 5 (25%)	 14 (93%) 1 (7%)	0.154	 3 (60%) 2 (40%)	 12 (9%) 1 (8%)	0.099
BA	7.8 (6 – 10.5)	7.5 (6 – 8.5)	0.124	9 (8 – 11)	8 (7.5 – 10.5)	0.043
BA/CA	1.07 (0.9 – 1.4)	1.01 (0.9 – 1.3)	0.059	0.98 (0.9 – 1.3)	0.97 (0.9 – 1.2)	0.238

*BA: Bone age, BMI: Body mass index, CA: Chronological age, SDS: Standard deviation score

0.200; 0.34 and 0.17, p_4: 0.522) (Table 2). There was no statistically significant difference between groups 3 and 4 in pubertal stages at presentation, year 1 and year 2 (p_1:0.438; p_2:0.046, p_3:0.299). The median value of BA change was 2 years in Group 3 and 2.4 years in Group 4 and was statistically similar (p:0.593). At the first year of follow-up, the median value of ΔBA/ΔCA was 0.37 in Group 1 and 1.56 in Group 2 and there was no significant difference between them (p:0.270). At the second year of follow-up, the median value of ΔBA/ΔCA was 1.21 in Group 3 and 0.93 in Group 4 and there was no statistically significant difference between them (p:0.724) (Table 2).

There was no statistically significant difference between the median values of PAH and TH-PAH between Group 1 and Group 2 at the first visit (163.7 and 161.2cm, p_1:0.953; 2.6 and 5.4cm p_2:0.529). In the first year of follow-up, PAH median values were similar in Group 1 and Group 2 with 163.7cm and 166.8cm, respectively, whereas TH - PAH median values were 4.3 cm in Group 1 and 8 cm in Group 2, and significantly higher in Group 2 (p: 0.009). At the second year of follow-up, the median PAH and TH-PAH values of Group 1 were 163.2 cm and 5cm, respectively, while the median PAH and TH-PAH values of Group 2 were 164.2cm and 3.5cm, respectively, with no significant difference (p_1: 0.563; p_2: 0.786) (Table 3).

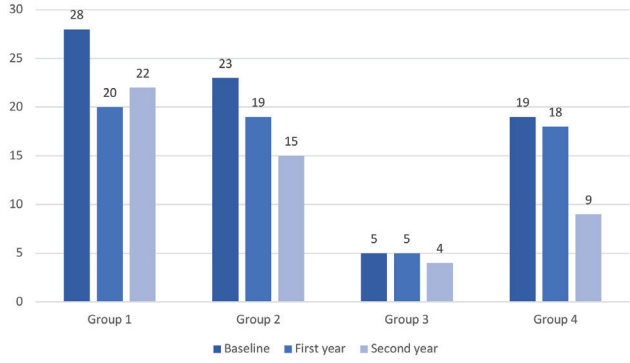

Figure 1. Number of cases in all groups by years

Group 3 had a median TH of 163.8 cm and a TH-SDS of 0.09, while Group 4 had a median TH of 160.3 cm and -0.47, with no significant difference between them (p_1:0.222, p_2:0.222). There was not significant difference between PAH and TH – PAH median values at the first visit between Group 3 and Group 4 (164.7 and 162.45cm, p_1:0.881; -0.9 and -0.95cm p_2:0.595). At the first year of follow-up, the median values of PAH and TH - PAH in Group 3 and Group 4 were 164.7cm and 162.4 cm; -2.3cm and 1cm, respectively, with no significant difference (p_1: 0.903; p_2: 0.734). In the second year of follow-up, the median PAH and TH-PAH values of Group 3 were 166.1cm and -0.7cm, respectively, while the median PAH and TH-PAH values of Group 4 were 160.7 cm and 1.6 cm, respectively, and no significant difference was found between them (p_1: 0.248; p_2: 0.513) (Table 3).

BMI-SDS values at admission were similar between Group 1 and Group 2 and between Group 3 and Group 4, and ΔBMI-SDS was similar during follow-up. The change in ΔBMI-SDS was similar in treated and untreated groups and no significant effect of treatment on BMI was found.

Table 2. Anthropometric change in all groups by years

	Group 1 median (min – max)	Group 2 median (min – max)	p	Group 3 median (min – max)	Group 4 median (min – max)	p
ΔHeight, cm	12.2 (6 – 21)	9.5 (4.5 – 21)	0.140	9 (6 – 14.3)	9.5 (5 – 17.7)	0.972
ΔHeight-SDS	0.1 (-2.3 – 1.5)	0.2 (-1.3 – 0.79)	0.501	0.03 (-1.2 – 0.4)	0.2 (-0.4 – 1.5)	0.082
ΔBMI, kg/m^2	2.2 (-4.3 – 5.6)	1.68 (-0.8 – 10.4)	0.399	2.9 (1.3 – 3.3)	1.3 (-1.3 – 4.7)	0.200
ΔBMI-SDS	0.16 (-2.7 – 1.5)	0.13 (-0.7 – 0.7)	0.520	0.34 (-0.05 – 0.6)	0.17 (-0.8 – 0.9)	0.522
ΔBA	2 (0.2 – 3.7)	1.3 (0.3 – 2)	0.231	2 (0.3 – 4)	2.4 (1.7 – 4.2)	0.593
ΔBA/CA (1st year)	1.09 (0 – 7.3)	0.66 (0 – 1.96)	0.297	0.37 (0 – 2.8)	1.56 (0.67 – 3.5)	0.270
ΔBA/CA (2nd year)	0.9 (0 – 1.7)	0.92 (0.6 – 1.1)	0.580	1.21 (0.1 – 2)	0.93 (0.2 – 1.7)	0.724

*BA: Bone age, BMI: Body mass index, CA: Chronological age, SDS: Standard deviation score

Table 3. PAH and TH - PAH values in all groups by years

	Group 1 median (min – max)	Group 2 median (min – max)	p	Group 3 median (min – max)	Group 4 median (min – max)	p
Baseline						
TH, cm	159.8 (151 – 168.5)	159 (147.5 – 168.5)	0.255	163,8 (157 – 169.5)	160.3 (154.5 – 167)	0.222
TH-SDS	-0.52 (-1.9 – 0.8)	-0.64 (-2.4 – 0.8)	0.265	0.09 (-1 – 0.97)	-0.47 (-1.3 – 0.66)	0.222
PAH, cm	163.7 (145.3 – 178.5)	161.2 (150.6 – 183.3)	0.953	164.7 (145 – 170.5)	162.45 (149.4 – 178.6)	0.881
TH – PAH, cm	2.6 (-12.5 – 13.8)	5.4 (-12.8 – 18.8)	0.529	-0.9 (-15 – 2.3)	-0.95 (-8.1 – 11.6)	0.595
First year						
PAH, cm	163.7 (151.9 – 177.5)	166.8 (155.3 – 174.4)	0.311	161.5 (151.8 – 166.5)	159.8 (148.2 – 169.2)	0.903
TH – PAH, cm	4.3 (-3.6 – 16.2)	8.05 (-1.8 – 15.1)	0.009	-2,3 (-8.2 – 4.5)	1 (-11.9 – 5.2)	0.734
Second year						
PAH, cm	163.2 (150.9 – 182.8)	164.2 (153.4 – 171)	0.563	166.1 (153.4 – 169.8)	160.7 (156.2 – 162.1)	0.248
TH – PAH, cm	5 (-5 – 22.8)	3.5 (-4.3 – 12.2)	0.786	-0,7 (-4.1 – 12.8)	1.6 (0.2 – 4.7)	0.513

*PAH: Predicted adult height, SDS: Standard deviation score, TH: Target height

Discussion

In this study, no statistically significant difference was found in the PAHs and TH-PAH changes of the treated and untreated groups during the follow-up period in all groups. BMI-SDS changes were also similar in the treated and untreated groups. Different results have been reported in various studies regarding the effect of treatment on height in children with CPP. Some studies have reported that treatment in cases of CPP improves PAH and final adult height, while other studies have reported that untreated girls can also reach their TH (9,18). It is thought that obtaining different results in different studies may be due to differences in the distribution of age groups, small number of cases and individual differences in the progression of puberty (19).

In a study conducted by Kauli et al. (20), 28 untreated children who started to show signs of puberty before the age of 8 and were diagnosed with CPP, were observed. Of these children 14 had slowly progressive puberty and 14 had rapidly progressive puberty. While the TH of children with slowly progressive puberty were 159.5 ± 6.6 cm, their FH reached 160.2 ± 7.1 cm. However, the subjects with rapidly progressing puberty could not catch up with their TH and their TH were 159.2 ± 5.9 cm while their FH reached 150.8 ± 4.3 cm. In another study in which cases were divided according to age groups, patients <6 years of age who received or did not receive treatment and patients >6 years of age who received or did not receive treatment were compared. When these cases were evaluated according to TH, it was observed that height gain in treated cases were 2.7 cm in the group aged <6 years and no height gain was observed with the treatment in the group aged >6 years (21).

Glab et al. (22) followed 40 girls with CPP at a mean age of 6.0 ± 1.9 years and started GnRHa therapy at a mean age of 7.5 ± 2.2 years. Among these patients, those who started treatment before the age of 7 years were found to benefit more from treatment in terms of final height. In a metanalysis, final height and PAH were assessed in 332 girls aged 7-10 years with and without treatment from six different studies. It was observed that there was no significant difference in final height between those who received treatment and those who did not (mean difference = 0.50 cm, 95% confidence interval = −0.72 to 1.73 cm, I^2 = 0%). In the PAH-based analysis, children were divided

into three groups: <155cm and <TH; <TH but >155cm and equal to TH. No difference was found between the groups in terms of final height averages (23). In another study in which one hundred and fifteen female patients with CPP were evaluated, the subjects were divided into three groups according to their age at the time of diagnosis (<6 years, 6-8 years, 8-9 years) and the effect of GnRHa treatment on FH was examined. They found TH 159.3 ± 5.0 cm, PAH 162 ± 7.3 cm and FH 162.8 ± 5 cm in the group below 6 years of age; TH 157.8 ± 5.2 cm, PAH 161.4 ± 6.5 cm and FH 157.9 ± 5.1 cm in the group between 6-8 years of age; TH 156.9 ± 4.7 cm, PAH 158.4 ± 5.8 cm and FH 153.9 ± 4.6 cm in the group between 8-9 years of age. As a result of this study, the positive effect of GnRHa treatment on FH was observed only in the <6y group and FH was found to be significantly higher than TH and PAH (24). In our study, PAH and TH - PAH values were similar in children aged 5-8 years and in children aged 8-10 years, who received and did not receive treatment during two year follow-up period.

Wang (25) explained that the prevalence of BMI, subcutaneous adipose tissue and obesity was higher in girls with early pubertal development than in girls with normal and late pubertal development. During lockdown at the time of the COVID pandemic, it has been observed that girls who were unable to move, confined to the house, and gained weight at this process, had earlier puberty and pubertal signs progressed much more rapidly (26). Our study shows similar findings with the literature and obesity rate was higher in Groups 1 and 2, which were younger age groups, compared to Groups 3 and 4.

There are different opinions about the effects of GnRHa treatment on BMI. Lee et al. (27) reported the changes in BMI-SDS of 38 girls with early puberty who received GnRHa treatment for 18 months. BMI-SDS increased from 0.58 ± 1.1 at baseline to 0.79 ± 0.84 after 12 months of treatment and to 0.96 ± 0.83 after 18 months of treatment. There was a significant increase in BMI-SDS with treatment. In a study by Wolters et al. (28), 92 children with CPP and early puberty receiving GnRHa treatment were assessed according to their weight status at baseline and change in weight with treatment. Surprisingly, BMI-SDS increased with treatment in normal-weight children (0.32 ± 0.66) but remained stable in overweight children (-0.02 ± 0.27). In addition, when BMI-SDS of 25 overweight children who were not treated with GnRHa was compared with 25 overweight children who received treatment, it was observed that BMI-SDS increased more in the untreated group at the end of the treatment period (+0.18 ± 0.22 in untreated group vs -0.02 ± 0.27 in treated group). None of the overweight children received any lifestyle modification intervention or any changes in their diet or exercise habits. As a result, GnRHa treatment was reported to have a positive effect on BMI-SDS in overweight children. Brito et al. (29) found that 42% of 45 female patients with PP who received GnRHa treatment were found to be overweight at the beginning of treatment, 47% at the end of treatment and 40% when they reached FH and it was reported that GnRHa treatment did not cause a significant increase in BMI. In our study, similar to the study of Brito et al. (29), BMI and BMI-SDS were similar between Groups 1 and 2 and between Groups 3 and 4 at baseline, and no significant difference was found between the groups with treatment.

Study Limitations

The limitations of the study were the retrospective design of the study, irregular follow-up of the patients and the small number of cases. It was planned to call back the cases to the hospital to evaluate their heights when they were thought to have reached the final height. However, since this period coincided with and after the COVID pandemic, a sufficient number of patients could not be reached and final heights could not be reported. Since the patients followed up had not yet reached FH, the effects of treatment were evaluated on the basis of PAH. PAH measurement is a BA-based measurement and the Greulich-Pyle atlas is used in BA assessment, and the fact that it is a subjective measurement method casts doubt on the reliability of the study on PAH.

Conclusion

In conclusion, since the changes in anthropometric values were similar in all groups in this study, it was concluded that treatment with GnRHa did not have a significant effect on anthropometric values in our limited patient group. Patients have been followed for a certain period of time and their development is not yet complete, so these results may be variable.

Ethics

Ethical Approval: Ethics committee approval was obtained from University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital on 17.07.2017 with protocol number 17.07.2017-2017/07/23.

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Footnotes

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