ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Final Height in GnRH Analogue Treatment in Girls Diagnosed with Early Puberty: Comparison with Untreated Controls

Erkence Puberte Tanılı Kızlarda GnRH Analog Tedavisinde Final Boy: Tedavi Edilmemiş Kontrollerle Karşılaştırma

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Abstract

Introduction: In this retrospective study, it was aimed to examine the effect of gonadotropin-releasing hormone (GnRH) analogue treatment on final height in girls diagnosed with early puberty (EP) between the ages of 8 and 10.

Materials and Methods: In the study, 87 girls who were diagnosed with EP and reached the final height were included. Two groups, those who received GnRH analogue treatment and those who did not, were formed. The average age, bone age, average height, height standard deviation score (SDS), body mass index SDS, target height, predicted adult height of the groups at the time of admission were calculated. The final height they reached and their menarche ages were noted.

Results: No difference was found between the groups in terms of average age, average height, height SDS, bone age, body mass index SDS at the time of admission. The target height, predicted adult height, final height and the SDS of these were similar in both groups. All cases in both groups reached the target height.

Conclusion: It was determined that the GnRH analogue treatment did not make a positive contribution to the final height in the EP group, who were between the ages of 8 and 10. Therefore, it can be recommended to use GnRHa treatment in EP patients with psychosocial problems and for delaying menarche.

Keywords
Early puberty, puberty, gonadotropin-releasing hormone analogue, final height

Öz

Giriş: Bu retrospektif çalışmada, 8-10 yaş arası erkence puberte (EP) tanısı konulan kız çocuklarında gonadotropin salgılatıcı hormon (GnRH) analog tedavisinin nihai boy üzerine etkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: EP tanısı alan ve final boya ulaşmış 87 kız olgu alındı. GnRH analog tedavisi alanlar ve almayanlar olmak üzere iki grup oluşturuldu. Grupların başvuru anındaki ortalama yaşı, kemik yaşı, ortalama boy, boy standart sapma skoru (SDS), vücut kitle indeksi SDS, hedef boy, tahmini erişkin boyu hesaplandı. Ulaştıkları son boy ve menarş yaşları not edildi.

Bulgular: Başvuru anında ortalama yaş, ortalama boy, boy SDS, kemik yaşı, vucut kitle indeksi SDS açısından gruplar arasında fark yoktu. Hedef boy, tahmini erişkin boy, final boy ve bunların SDS'leri her iki grupta benzerdi. Her iki gruptaki tüm olgular hedef boya ulaştı.

Sonuç: GnRH analog tedavisinin 8-10 yaş EP grubunda final boya olumlu bir katkı yapmadığı tespit edildi. Bu nedenle, GnRHa terapisinin EP'de psikososyal zorlukları olan olgulara ve menarşın geciktirilmesi için kullanılması önerilebilir.

Anahtar kelimeler
Erkence puberte, puberte, gonadotropin salgılatıcı hormon analoğu, final boy

Received/Geliş Tarihi : 12.12.2021
Accepted/Kabul Tarihi : 29.05.2022

DOI:10.4274/jcp.2022.54280

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Introduction

Central precocious puberty is the early development of secondary sexual characteristics before the age of eight in girls and nine in boys, due to the early activation of the hypothalamic-pituitary gonadal (HPG) axis. This condition may lead to acceleration in the bone maturation and premature closure of growth plates, resulting in remaining short after reaching the final adult height (FH) (1,2). Early puberty (EP) is the presence of clinical and auxological findings of pubertal development in girls between the ages of 8 and 10. It manifests itself with the characteristics of precocious puberty. In girls, breast development, increased growth rate and advanced bone age (BA) occur. There is an increase in the basal and stimulated gonadotropins (3). Although various age ranges have been specified for EP (4-6), it is a term mostly used for puberty that starts between the ages of 8 and 10 (6-8).

Gonadotropin-releasing hormone analogues (GnRHa) have been used for many years in the treatment of precocious puberty. GnRHa treatment suppresses the HPG axis and reduces hormones to the prepubertal level. Thus, it is believed to improve the FH by slowing the maturation of BA (9-11). In the literature reviews, it has been stated that GnRHa treatment is beneficial for the FH, especially in cases whose pubertal findings start before the age of 6 (7,12).

It has been reported that different results have been obtained regarding GnRHa treatment in cases between the ages of six and eight (4,10,13,14).

However, it is stated that it does not contribute to the FH in cases who receive GnRHa treatment after the age of 8 (6,15). Although it has been accepted that it does not improve the FH after the age of eight, it has been reported that GnRHa treatment can still be used for the psychosocial problems due to adolescence (16,17).

In this study, it was aimed to retrospectively compare the final heights (FH) of the two groups, who received GnRHa treatment and who did not, in girls diagnosed with EP between the ages of 8 and 10.

Materials and Methods

In this study, 87 female cases diagnosed with EP between the ages of 8 and 10 and reached the FH, who were admitted to Dicle University Faculty of Medicine Pediatric Endocrinology Polyclinic between 2010 and 2020, were included. Patients with onset of puberty after the age of 8 were included in the study. Patients with breast development, increased growth rate, advanced BA, pubertal response to the basal luteinizing hormone (LH) or GnRH-stimulated LH, signs of precocious puberty and who reached the FH were included in the study (3).

The medical records of the cases were examined retrospectively. Those who received gonadotropin-releasing hormone analogue treatment were named group 1 (n=57), and those who did not receive GnRHa treatment were named group 2 (n=30). Cases with a chronic disease, history of prematurity, organic brain lesions, congenital adrenal hyperplasia or other endocrinological problems were excluded from the study.

The age at the time of admission, body weight (BW), BW standard deviation score (SDS), height, height SDS, body mass index (BMI) and the BMI SDS of all of the cases were recorded. The height, weight, BMI and SDS were calculated according to the national data and using the "Child Metrics" software (18,19). The BW was measured using the SECA 767 scale (Carson City, NV, USA) and height was measured using the Harpenden stadiometer. The BMI was calculated with the formula BMI = weight (kg) x height^2 (m^2).

The stage of puberty, target height (TH) and TH-SDS, BA, predicted adult height (PAH) and PAH-SDS of the cases at the time of admission were calculated. In addition, the FH they reached and the FH-SDS were noted. The puberty stages of the cases were evaluated according to the Tanner scale (20).

The TH and TH-SDS were calculated by measuring the heights of the parents. The TH was calculated using the formula: TH = mid-parental height - 6.5 cm (8). Radiography of the left hand wrist was performed on all patients. The BA (21) was calculated with the Greulich-Pyle atlas, and the PAH (22) was calculated with the Bayley-Pinneau method. The hand-wrist radiographs of all patients were evaluated by the same pediatric endocrinologist. The delta height SDS was obtained by calculating the difference between the FH-SDS, and the height SDS at the start of the treatment.

The follicle stimulating hormone (FSH), LH and estradiol (E2) levels of the patients included in the study were measured. The hormone measurements were evaluated by collecting venous blood samples

from the patients in the morning after an eight-hour fast. Immunochemiluminometric assay kits were used to measure the follicle stimulating hormone, LH and E2 (ARCHITECT System, Abbott Laboratory Diagnostics, USA) levels. The HPG axis was thought to be active in cases with a basal LH level of ≥0.3 IU/L (8,23).

GnRH stimulation test was performed by injecting gonadorelin acetate intravenously between 8.00-8.30 in the morning for the evaluation of EP in patients with a basal LH level of <0.3I U/L. The HPG axis was considered to be active in patients with a peak LH level of ≥5 IU/L (23,24).

All cases in group 1 received 3.75 mg depot leuprolide acetate treatment every 28 days. The cases in group 2 did not receive any treatment. The patients who received treatment were followed up in 3-month periods. In the group who received treatment, GnRHa-stimulated LH levels of <4 mIU/mL and regression of breast development were considered as responses to the treatment (25). The HPG axis was suppressed by treatment in patients in Group 1. None of the patients received an increase in the dose or were excluded from the study. The BA was calculated every 12 months. The treatment was discontinued when the chronological age was 11 and the BA was 12 (15). The menarche ages of all patients whose follow-up was continuing were recorded. Patients with a BA of 15 and bone growth of <1 cm/year were considered to have reached the FH (8,26,27).

The approval for this study was obtained from the Ethics Committee of Dicle University Faculty of Medicine (approval number: 2021/173 date: 25.03.2021).

Statistical Analysis

The statistical analysis of the obtained results was performed using the SPSS 21.0 (Statistical Package for the Social Sciences-IBM®, Chicago, IL, USA) statistical software package. Whether the variables were normally distributed or not was evaluated using the Shapiro-Wilk test. Descriptive statistics for continuous variables were presented as mean ± standard deviation, minimum and maximum values, while categorical variables were expressed as numbers and percentages. In the comparison of two independent groups, Student's t-test was used. In order to determine whether there was a relationship between two or more variables, and if there was, the degree of this relationship, a correlation analysis was performed. A p value of <0.05 was considered significant in the statistical evaluation.

Results

Of the 87 patients included in the study, 39 (44.8%) were diagnosed using the GnRH stimulation test, while 48 (55.2%) were diagnosed according to the basal LH levels. Of the 87 cases included in the study, 57 (65.5%) were included in group 1 and 30 (34.5%) were included in group 2. The anthropometric and demographic characteristics of the groups are summarized in Table 1.

In group 1, 27 (47.4%) of the cases had Tanner stage 2 breast development and 30 (52.6%) had Tanner stage 3 breast development at the time of admission. Pubarche was also present in 32 (56.1%) of the patients in group 1. Of the cases in group 2, 19 (63.3%) presented with Tanner stage 2 and 11 (36.7%) presented with Tanner stage 3. None of our patients presented with menarche. No statistically significant difference was found between the groups in terms of Tanner staging (p=0.156). The Tanner stage, age of menarche, FSH, LH, E2, peak LH and LH/FSH values of the groups were compared. No statistically significant difference was observed between the groups in terms of FSH, E2, peak LH, LH/FSH ratios and Tanner stages at the time of admission (p>0.05). There was a significant difference between the groups in terms of basal LH levels (p=0.033). In group 1, the basal LH levels were higher (Table 1).

The average age of the cases in Group 1 at the time of admission was 8.75±0.44 years, the average height was 133.46±5.96 cm and the average BA was 10.12±0.86 years. The average age of the cases in group 2 at the time of admission was 8.80±0.53 years, the average height was 133.35±6.84 cm, and the average BA was found to be 9.96±0.96 years. The average age, height, height SDS, BA, BMI-SDS, PAH, PAH-SDS at the time of admission were similar between the groups.

The average FH was 158.62±6.13 cm in group 1, while it was found to be 157.59±5.76 cm in group 2. There was no statistically significant difference between the groups in terms of FH (p=0.43). There

Table 1. Comparison of the demographic characteristics and anthropometric data of the study groups			
	Group 1 (n=57)	Group 2 (n=30)	p value
Age at presentation (year)	8.75±0.44	8.80±0.53	0.70[a]
Height at presentation (cm)	133.46±5.96	133.35±6.84	0.93[a]
Height presentation SDS	0.44±0.97	0.38±1.0	0.79[a]
Weight presentation SDS	0.35±1.04	0.24±1.00	0.63[a]
Presentation BMI SDS	0.199±1.00	0.120±0.908	0.71[a]
Bone Age at presentation (year)	10.12±0.86	9.96± 0.96	0.45
Menarche(years)	11.9±0.71	11.1±0.85	<0.01[a]
Basal LH	0.43 (0.13-1.28)	0.20 (0.1-0.64)	0.033[b]
Basal FSH	4.03 (2.39-5.02)	3.66 (2.18-4.57)	0.401[b]
Basal estradiol (E2)	13.46 (5-21.79)	10.97 (5-16.07)	0.539[b]
Pik LH	6.27 (0-10.37)	6.10 (0-8.33)	0.529[b]
LH/FSH	0.60 (0-0.97)	0.65 (0-0.81)	0.974[b]
Tanner stage 2/3	27/30	19/11	0.156[c]

[a]:Student's t-test, [b]:Mann-Whitney U test, [c]:Chi-square test parameters are given as mean ± standard deviation (SD) or median (25-75th percentile). BMI: Body mass index, SDS: Standard deviation score, LH: Luteinizing hormone, FSH: Follicle stimulating hormone

Table 2. The target height, predicted adult height and final height of the study groups			
	Group 1	Group 2	p value
Target height (cm)	158.29±3.87	157.68±5.06	0.56
Target height SDS	-0.81±0.66	-0.92±0.86	0.55
Predicted adult height (cm)	156.61±7.47	157.75±6.50	0.46
Predicted adult height SDS	-1.10±1.27	-0.90±1.10	0.45
Final height (cm)	158.62±6.13	157.59±5.76	0.43
Final height SDS	-0.16±0.96	-0.04±1.08	0.61

SDS: Standard deviation score

was no significant difference between the groups in terms of TH (p=0.56) (Table 2). All cases in both groups reached the TH.

No statistical difference was found between the FH and the TH and PAH in Group 1 (158.62±6.13 cm, 158.29±3.87 cm and 156.61±7.47 cm, respectively). In group 2, there was also no difference between the FH and the TH and PAH (157.59±5.76 cm, 157.68±5.06 cm and 157.75±6.50 cm, respectively). In Group 1, there was a difference of 1.68 cm between the PAH and the TH, and a difference of 0.33 cm between the FH and the TH. In group 2, a difference of 0.09 cm between the FH and the TH occurred. The average duration of treatment in group 1 was 2.22±0.58 years. Menarche occurred in the cases an average of 11.1 (range: 3-24) months after the discontinuation of treatment. In group 1, the mean age of menarche was 11.9±0.71 years, and in group 2, 11.1±0.85 years. There was a significant difference between the groups in terms of menarche age (p<0.01). In group 1, the lowest age of menarche was 10.5, and the highest age of menarche was 13.5 years. In group 2, the lowest age of menarche was 10, and the highest age of menarche was 12.5 years.

In the general population, there was a positive correlation between the heights of the cases at the time of admission and the FH (r=0.624, p=<0.01), and between the TH (r=0.56, p=<0.01) and the PAH (r=0.703, p=<0.01). No correlation was found between the other parameters (Table 3). The delta height SDS was calculated as -0.60±0.80 in group 1 and as -0.43±0.67 in group 2. The groups were similar in terms of delta height SDS (r=0.29, p=0.27).

Table 3. Correlation of the final heights of the cases with other parameters		
	r value	p value
Height at presentation	0.624	<0.01
Bone age	-0.026	0.81
Menarche	0.058	0.594
Target height	0.56	<0.01
Predicted adult height	0.703	<0.01

Discussion

In early puberty, Tanner stage 3 can be reached much earlier due to the acceleration of puberty. Rapid development of secondary sexual characteristics in children can lead to poor social adaptation, psychological stress, emotional disorders, and remaining short after reaching the FH (15,28,29). In the literature, there are studies evaluating the effectiveness of the GnRHa treatment in patients whose pubertal findings started between the ages of 8 and 10. However, for this age group, there are only a few studies that include a control group (6,8,15). We compared the two groups, those who received GnRHa treatment and those who did not receive GnRHa treatment, among the patients who were admitted between the ages of eight and ten and were thought to have EP. We determined that the FH of the groups reached the TH and there was no significant difference between the groups in terms of FH.

Since the start of the therapeutic use of gonadotropin-releasing hormone analogues, their effect on FH has aroused interest. Until today, many studies have examined the effect of GnRHa use on FH in different age groups (4,11,12,25,30). Kletter and Kelch reported that in patients above the age of 6 and had an onset of puberty, there was no significant difference in terms of FH between those who received treatment and those who did not (11). In their series of 115 cases, Lazar et al. (12) examined the height gain of the patients, and stated that the use of GnRHa, especially before the age of 6, had an effect on the height. It was determined that there was a partial height gain between the ages of 6 and 8, but the treatment had no effect on the FH in girls between the ages of 8 and 9. In studies conducted by Cassio et al. (4) and Savaş-Erdeve et al. (30) on cases between the ages of 7.5 and 8.5, and 7 and 8.5 respectively, the cases that received and did not receive GnRH treatment were observed until they reached the FH, and no difference was observed between the groups in terms of FH.

It was observed that similar results were obtained especially in studies including cases above the age of 8 (6,15,31). In a meta-analysis of six studies recently carried out by Franzini et al. (31), 332 female cases between the ages of 7 and 10 were examined. In this meta-analysis, it was stated that no difference was found between the FH of the patients who received and did not receive GnRHa treatment. In a similar study, two groups consisting of 63 patients and 63 controls between the ages of 8 and 9 were compared. In the study, it was found that the FH of the girls who received and did not receive GnRH treatment were similar (157.26±6.16 and 156.66±5.70 cm, respectively). In the study, it was stated that the similar height gain of the groups was not dependent on the duration of puberty and the rate of pubertal development. It was stated that pubertal growth potential and FH are probably determined at the beginning of pubertal development (15). In a study conducted by Bouvattier et al. (6), a patient and a control group were formed with cases above the age of 8, and it was found that there was only a 1.44 cm difference in terms of FH. In another study, it was reported that after the GnRHa treatment administered to 44 EP patients between the ages of 8 and 10, the patients reached the TH, therefore the treatment made a significant contribution of 4.13 cm to the FH (8). In our study, we found that there was a difference of approximately 1.03 cm between the FH of the two groups. However, this difference was not statistically significant. In addition, it was determined that the FHs of 57 patients who received GnRHa treatment reached the TH. In our study, no difference was found between the FH and TH in the group that received GnRH analogue treatment and in the group that did not receive treatment. Since the FH and the TH were almost the same, it was thought that the GnRH analogue treatment did not contribute to the height in patients between the ages of 8 and 10.

In previous studies conducted on precocious puberty, it was stated that the most important parameters affecting the FH were the height at the onset of puberty and the TH (30,32). In our study, there was a positive correlation between the FH and the TH and PAH. Therefore, the taller the case at the onset of puberty, the higher the FH will be.

In patients who receive gonadotropin-releasing hormone analogue treatment, after the treatment is discontinued, the gonadal functions are restored and menstrual cycles begin. Studies have reported that menarche occurs approximately 1-1.5 years after the discontinuation of treatment (6,15,32-34).

In our study, it was observed that in the cases who received GnRHa treatment, menarche occurred an average of 11.1 months after the discontinuation of treatment. In the group that received gonadotropin-releasing hormone analogue treatment, menarche occurred at a later age compared to the group that did not receive treatment. It was thought that GnRH analogue treatment caused a delay in the age of menarche in these patients. In studies in the literature, generally, no height gain has been observed following the GnRHa treatment after the age of 8. However, it has been reported that the treatment in this age group can delay the age of menarche and reduce the psychological effects.

Study Limitations

There were some limitations to our study: Our study was designed retrospectively. The sample size constituting the patient and control groups was not sufficient.

Conclusion

This study, it was observed that the GnRHa treatment did not make a positive contribution to the FH in cases who were between the ages of 8 and 10. No difference was found between the groups in terms of FHs. The FHs of the cases in both groups reached the TH. The GnRHa analogue treatment slowed the rate of pubertal development and delayed the age of menarche. Therefore, GnRHa treatment in EP can be used for psychosocial problems that may be caused by rapid pubertal development.

Ethics

Ethics Committee Approval: The approval for this study was obtained from the Ethics Committee of Dicle University Faculty of Medicine (approval number: 2021/173, date: 25.03.2021).

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Chen M, Eugster EA. Central Precocious Puberty: Update on Diagnosis and Treatment. Paediatric Drugs 2015;17:273-81.
2. Grumbach MM, Styne DM. Puberty: Ontogeny, neuroendocrinology, physiology, and disorders. In: Williams RH, Foster DW, Kroenenberg H, Larsen PR, Zorab R,editors. Williams Textbook of Endocrinology 9nd ed. Philadelphia, Saunders, 1998:1509-625.
3. Pagani S, Calcaterra V, Acquafredda G, Montalbano C, Bozzola E, Ferrara P, et al. MKRN3 and KISS1R mutations in precocious and early puberty. Ital J Pediatr 2020;46:39.
4. Cassio A, Cacciari E, Balsamo A, Bal M, Tassinari D. Randomised trial of LHRH analogue treatment on final height in girls with onset of puberty aged 7.5-8.5 years. Arch Dis Child 1999;81:329-32.
5. Lebrethon MC, Bourguignon JP. Management of central isosexual precocity: diagnosis, treatment, outcome. Current Opinion in Pediatrics 2000;12:394-9.
6. Bouvattier C, Coste J, Rodrigue D, Teinturier C, Carel JC, Chaussain JL, et al. Lack of effect of GnRH agonists on final height in girls with advanced puberty: a randomized long-term pilot study. J Clin Endocrinol Metab 1999;84:3575-8.
7. Mul D, de Muinck Keizer-Schrama SM, Oostdijk W, Drop SL. Auxological and biochemical evaluation of pubertal suppression with the GnRH agonist leuprolide acetate in early and precocious puberty. Horm Res 1999;51:270-6.
8. Lin YC, Lin CY, Chee SY, Yen HR, Tsai FJ, Chen CY, et al. Improved final predicted height with the injection of leuprolide in children with earlier puberty: A retrospective cohort study. PLoS One 2017;3:12:e0185080.
9. Willemsen RH, Elleri D, Williams RM, Ong KK, Dunger DB. Pros and cons of GnRHa treatment for early puberty in girls. Nat Rev Endocrinol 2014;10:352-63.
10. Ságodi L, Sólyom E, Lombay B, Almási A, Vámosi I. Effect of treatment with gonadotropin releasing hormone analogues in girls with idiopathic central precocious puberty. Orv Hetil 2012;18:418-24.
11. Kletter GB, Kelch RP. Clinical review 60: Effects of gonadotropin-releasing hormone analog therapy on adult stature in precocious puberty. J Clin Endocrinol Metab 1994;79:331-4.
12. Lazar L, Padoa A, Phillip M. Growth pattern and final height after cessation of gonadotropin-suppressive therapy in girls with central sexual precocity. J Clin Endocrinol Metab 2007;92:3483-9.
13. Klein KO, Barnes KM, Jones JV, Feuillan PP, Cutler GB Jr. Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. J Clin Endocrinol Metab 2001;86:4711-6.
14. Korkmaz O, Sari G, Mecidov I, Ozen S, Goksen D, Darcan Ş. The Gonadotropin-Releasing Hormone Analogue Therapy May Not Impact Final Height in Precocious Puberty of Girls With Onset of Puberty Aged 6-8 Years. J Clin Med Res 2019;11:133-6.
15. Lazar L, Kauli R, Pertzelan A, Phillip M. Gonadotropin-suppressive therapy in girls with early and fast puberty affects the pace of puberty but not total pubertal growth or final height. J Clin Endocrinol Metab 2002;87:2090-4.
16. Mercader-Yus E, Neipp-López MC, Gómez-Méndez P, Vargas-Torcal F, Gelves-Ospina M, Puerta-Morales L, et al. Anxiety, Self-esteem and Body Image in Girls with Precocious Puberty. Rev Colomb Psiquiatr 2018;47:229-36.

17. Menk TAS, Inácio M, Macedo DB, Bessa DS, Latronico AC, Mendonca BB, et al. Assessment of stress levels in girls with central precocious puberty before and during long-acting gonadotropin-releasing hormone agonist treatment: a pilot study. J Pediatr Endocrinol Metab 2017;30:657-62.
18. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, et al. Referance Values for Weight, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol 2015;7:280-93.
19. Demir K, Özen S, Konakçı E, Aydın M, Darendeliler F. A Comprehensive Online Calculator for Pediatric Endocrinologists: ÇEDD Çözüm/TPEDS Metrics. J Clin Res Pediatr Endocrinol 2017;9:182-4.
20. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44:291-303.
21. Greulich WW, Pyle EI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford: Stanford University Press, 1966.
22. Bayley N, Pinneau S. Tables for predicting adult height from skeletal age: revised for use with Greulich-Pyle hand standards. J Pediatr 1952;40:423-41.
23. Neely EK, Hintz RL, Wilson DM, Lee PA, Gautier T, Argente J, et al. Normal ranges for immunochemiluminometric gonadotropin assays. J Pediatr 1995;127:40-6.
24. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR; ESPE-LWPES GnRH Analogs Consensus Conference Group, Antoniazzi F, Berenbaum S, Bourguignon JP, Chrousos GP, Coste J, Deal S, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123:e752-62.
25. Onat PŞ, Erdeve ŞS, Çetinkaya S, Aycan Z. Effect of gonadotropin-releasing hormone analog treatment on final height in girls aged 6-10 years with central precocious and early puberty. Turk Pediatri Ars 2020;55:361-9.
26. Carel JC, Roger M, Ispas S, Tondu F, Lahlou N, Blumberg J, et al. Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. French study group of Decapeptyl in Precocious Puberty. J Clin Endocrinol Metab 1999;84:1973-8.
27. Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R, et al. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. J Clin Endocrinol Metab 2008;93:190-5.
28. Głąb E, Wikiera B, Bieniasz J, Barg E. The Influence of GnRH Analog Therapy on Growth in Central Precocious Puberty. Adv Clin Exp Med 2016;25:27-32.
29. Sun L, Guo X, Zhang J, Liu H, Xu S, Xu Y, et al. Gender specific associations between early puberty and behavioral and emotional characteristics in children. Zhonghua Liu Xing Bing Xue Za Zhi 2016;37:35-9.
30. Savaş-Erdeve Ş, Şıklar Z, Hacıhamdioğlu B, Kocaay P, Çamtosun E, Öcal G, et al. Gonadotropin-Releasing Hormone Analogue Treatment in Females with Moderately Early Puberty: No Effect on Final Height. J Clin Res Pediatr Endocrinol 2016;8:211-7.
31. Franzini IA, Yamamoto FM, Bolfi F, Antonini SR, Nunes-Nogueira VS. GnRH analog is ineffective in increasing adult height in girls with puberty onset after 7 years of age: a systematic review and meta-analysis. Eur J Endocrinol 2018;179:381-90.
32. Oostdijk W, Rikken B, Schreuder S, Otten B, Odink R, Rouwé C, et al. Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. Arch Dis Child 1996;75:292-7.
33. Chen SK, Fan X, Tang Q. Impact of gonadotropin-releasing hormone analogs treatment on final height in girls with central precocious puberty. Zhongguo Dang Dai Er Ke Za Zhi 2009;11:374-6.
34. Lee HS, Yoon JS, Park KJ, Hwang JS. Increased final adult height by gonadotropin-releasing hormone agonist in girls with idiopathic central precocious puberty. PLoS One 2018;13:e0201906.