Original Article

The Effects of Gonadotropin-Releasing Hormone Analog and a Combination of Gonadotropin-Releasing Hormone Analog and Recombinant Human Growth Hormone on Adult Height in Girls with Early Puberty

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Abstract

Background: Early puberty (EP) is due to the activation of gonadotropin-releasing hormone (GnRH) pulse generator in lower ages; EP may be a potential cause for impairment of adult height, leading to short stature. The aim of this study was to determine the effects of GnRH analog (GnRHa) and GnRHa plus recombinant human growth hormone (rhGH) treatment on final height in healthy girls with EP. **Materials and Methods:** Fifty EP girls (sexual maturity rating: 2–3) with chronological age (CA) 9.22 ± 0.56 and bone age (BA) 9.74 ± 0.59 years were treated with GnRHa (Triptorelin) at a dose of 100 μg/kg body weight (BW) as intramuscular every 28 days for 2.82 ± 0.57 years; 45 EP girls with CA 9.84 ± 0.57 and BA 10.14 ± 1.02 years were also treated with the same GnRHa plus rhGH (Norditropin) at a dose of 0.1 unit/kg BW daily for 6 days in a week for 2.55 ± 0.6 years. In the control group, 33 EP girls followed for the same period without treatment. Height, weight, and body mass index of girls and parents were assessed. Predicted adult height (PAH) at the start and the end of the study and target height were assessed. **Results:** PAH at the end of the study in the GnRHa group was not different with untreated girls. PAH at the end of the treatment in GnRHa plus rhGH group was significantly higher than both untreated and GnRHa group. PAH at the end of therapy in GnRHa plus rhGH group was significantly more than their target height. **Conclusion:** GnRHa therapy has a benefit effect in achievement of target height. Combination therapy with GnRHa plus rhGH increased their PAH more than both untreated and GnRHa groups.

Keywords: *Early puberty, final height, gonadotropin-releasing hormone analog, mid parental height, predicted adult height, recombinant human growth hormone*

Introduction

Puberty may be defined as a life span in which a transfer occurs through childhood to adult and individuals attain potential of fertility. The main changes of puberty are due to an endocrine change in the activity of hypothalamus; the first step is the reactivation of gonadotropin-releasing hormone (GnRH) neurons to secrete GnRH in a pulsatile manner and subsequently the activation of hypothalamus–pituitary–gonad (HPG) axis.[1]

During the process of puberty, several biological changes occur in the body, especially height growth, development of secondary sexual characteristics, growth and mineralization of bones, maturation of the central and peripheral nervous system, and growth and maturation of other organs such as kidney and heart.[1]

The onset of puberty depends on several factors from genetic to environment and geographical areas, diet, and fat composition of the body. In girls, lean body mass starts to increase at 6 years, and in boys, at 9.5 years; increase in lean body mass is the earliest change in body composition at puberty.[2,3] Pubertal growth spurt as the highest growth rate during puberty may be detected in girls before the onset of secondary sexual characteristics, while peak height velocity in girls occurs at 11.5 years.[3,4]

Early puberty (EP) is due to the activation of GnRH pulse generator in lower ages, occurring often in girls;[5] EP may be a potential cause for impairment of adult height. In EP girls, the pubertal onset

How to cite this article: Hajzadeh G, Ghaemi N, Hadjzadeh MA, Noroozi S, Morovatdar N. The effects of gonadotropin-releasing hormone analog and a combination of gonadotropin-releasing hormone analog and recombinant human growth hormone on adult height in girls with early puberty. Adv Biomed Res 2019;8:57.

Received: May, 2019. Accepted: August, 2019.

Access this article online

Website: www.advbiores.net

DOI: 10.4103/abr.abr_121_19

Quick Response Code:

is slightly advanced, leading to a short stature which may impose psychological problem both in children and parents.[6]

GnRH analogs are the drug of choice in treatment of children with central precocious puberty (CPP) and also are used in treatment of girls with EP; although in this regard, some available data have reported minimal change on growth outcome in EP girls.[7,8] Retarded GnRH analogs are used to induce a biochemical and clinical suppression of HPG axis leading to a retardation and/or delay in bone age (BA) and secondary sexual characteristics, decrease pubertal progress, and inhibit advanced maturation of epiphyseal growth plate[5] giving a longer time for growth potential.

Recombinant human growth hormone (rhGH) is also used in treatment of several diseases in children including growth hormone deficiency, small for gestational age children, idiopathic short stature,[1,9-11] and EP children.

Combination therapy with GnRH analog (GnRHa) and rhGH causes a delay in the progression of BA and brings about more time for rhGH to insert its positive effect on bone growth, although the efficacy of this treatment for EP children has been questioned both in case of the poor impact on final height and also from the cost-benefit point of view.[5,8]

The aim of this study was to evaluate the impact of GnRHa alone and GnRHa combined with rhGH in EP girls and compare the results with the control group.

Materials and Methods

This cohort study was conducted on girls with the diagnosis of EP in the outpatient clinic of the Department of Pediatric Endocrinology and Metabolism in Imam Reza Hospital, Medical School of Mashhad University of Medical Sciences, Iran. Girls aged 8–10.5 years with sexual maturity rating (SMR) 2–3 were included in the study. Clinical evaluation and complete physical examination were done, and biochemical parameters including serum levels of luteinizing hormone, follicle-stimulating hormone, estradiol, testosterone, dehydroepiandrosterone sulfate, and androstenedione were measured by routine laboratory methods.

An X-ray from the wrist of the left hand was also taken by an expertise radiologist, and BA was assessed by Greulich and Pyle Method. Girls whose predicted adult height (PAH) by the method of Bayley and Pinneau were <155 cm were included in the study. All subjects were in a state of normal health without congenital abnormalities, psychomotor or genetic diseases, brain tumors, kidney and heart diseases. Precocious puberty (onset of puberty before 8 years); congenital adrenal hyperplasia and other endocrine and metabolic disorders also were excluded.

Anthropometric measurement

Girls' heights and parental heights were measured at the standing position by a Seca stadiometer (Seca, Germany) by the nearest 0.2 cm; the weights for all children and parents were also measured by an electronic sensitive scale (Seca, Germany) to 0.1 g; body mass index (BMI) was calculated as weight/height^2 (kg/m^2). PAH and the route of drug administration and other aspects of drug therapy were described for children and parents. Girls whose parents refused drug therapy served as a control group (n = 33). Other girls were divided into GnRHa group (n = 50) and GnRHa plus rhGH group (n = 45).

In this study, GnRHa, Diphereline, was administered at a dose of 100 μg/kg body weight (BW) as intramuscular every 28 days; rhGH, NordiLet pen, was administered subcutaneously at a dose of 0.1 unit/kg BW daily for 6 days in a week. Height, weight, and clinical observation for the evaluation of secondary sexual characteristics by SMR or Tanner stages were assessed every 3–4 months for all girls in three groups during the study. Follow-up duration for each girl was dependent on the growth rate in the present visit compared to the last one; treatment was stopped for all girls when the growth rate was <4 cm/year.

Ethical approval

This study was approved by the Ethical Committee of Medical School of Mashhad University of Medical Sciences (IR.MUMS.fm.Rec. 1396.661); informed consent was also obtained from the parents of all girls participating in the study.

Statistical analysis

Software SPSS version 22 (Stanford University, Chicago, USA) was used to analyze data; data were expressed as mean ± standard deviation (SD); normal distribution of data was assessed by Kolmogorov–Smirnov test; one-way ANOVA was used for comparison between three groups; and *post hoc* Tukey test was used for comparison between two groups. Kruskal–Wallis test and regression analysis also were used in this study. $P < 0.05$ was considered statistically significant.

Results

Initial clinical characteristics of the study for GnRHa treated and control groups are demonstrated in Table 1. Chronological age (CA), height, and height SD score (SDS) were significantly higher in the control group than the GnRHa-treated group (ALL $P < 0.001$). Weight was also higher in control than the GnRHa group by $P = 0.01$, while BMI, BA, target height, and PAH at the start of the study were not different between GnRHa-treated and control groups [Table 1].

At the end of the study, PAH was not statistically different between GnRHa-treated and control groups [Table 1].

Initial PAH in GnRHa-treated group was 153.44 ± 5.24, and at the end of the study, it reached to 157.50 ± 3.41 which is significantly higher than the beginning ($P < 0.001$).

The target height in this group was 157.56 ± 4.42 which is not different with the PAH at the end of the study; hence, this group reached their target height [Figure 1]. In control group, PAH at the beginning of the study was 154.76 ± 5.14, and at the end of the study, it was 157.70 ± 5.38 which is significantly higher than the beginning ($P < 0.001$). PAH at the end of the study in this group was significantly lower than the target height (158.45 ± 5.8) by $P = 0.029$ [Figure 2].

Baseline clinical characteristics for combined therapy with GnRHa and rhGH in comparison with control group are presented in Table 2. CA was not different between two groups, but height, height SDS, and weight were significantly lower in combined treated group than the control by $P < 0.001$ to $P = 0.006$, respectively. BA, target height, and PAH at the beginning of the study were not different between two groups. PAH in GnRHa plus rhGH-treated groups at the end of the study was 158.44 ± 3.55 which is significantly higher than the control group (157.70 ± 5.38) by $P = 0.005$ [Table 2]. In combined treated group, the baseline PAH was 151.36 ± 6.17 and cached up to 158.44 ± 3.55 at the end of the study which is significantly higher than the beginning by $P < 0.001$; PAH in this group at the end of the study is also higher than the target height (155.55 ± 5.42) by $P = 0.035$ [Figure 3].

Initial clinical characteristics between GnRHa plus rhGH treated group and GnRHa-treated group are compared in Table 3. CA in combined treated group was significantly higher than GnRHa treated group by $P < 0.001$, while no difference was found in height, height SDS, weight, BMI, target height, and PAH at the baseline between two groups. BA in combined treated group was 10.14 ± 1.02 years which is significantly higher than the GnRHa-treated group (9.74 ± 0.59 years) by $P = 0.03$. At the end of the study, PAH in combined treated group was 158.44 ± 3.55, and in GnRHa treated group, it was 157.50 ± 3.41 which is significantly higher than the GnRHa treated group by $P = 0.008$ [Table 3].

Table 1: Clinical characteristics of gonadotropin-releasing hormone analog-treated girls in comparison to controls

Clinical characteristics	GnRHa-treated girls	Controls	*P*
Age (years)	9.22±0.56	9.66±0.74	<0.001
Height (cm)	132.20±5.14	140.9±9.11	<0.001
Height SDS	−0.3±0.7	0.62±1.2	<0.001
Weight (kg)	32.67±5.49	37.11±8.45	0.01
BMI (kg/m^2)	18.64±2.39	18.61±3.19	NS
Bone age (years)	9.74±0.59	10.02±0.96	NS
Target height (cm)	157.56±4.42	158.45±5.80	NS
PAH_1 (cm)	153.44±5.24	154.76±5.14	NS
PAH_2 (cm)[a]	157.50±3.41	157.70±5.38	NS

[a]By regression (covariance) analysis and removing the conflicting variables (P=0.44). . Target height is equal to mid parental height. n=33 in control group, n=50 in GnRHa-treated group. NS: Nonsignificant difference (P>0.05), BMI: Body mass index, PAH: Predicted adult height, PAH_1: PAH at the start of the study, PAH_2: PAH at the end of the study, GnRHa: Gonadotropin-releasing hormone analog, SDS: Standard deviation score

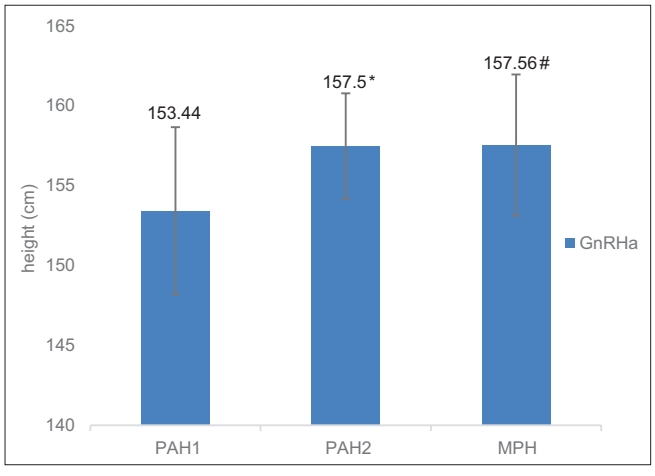

Figure 1: Predicted adult height 1, predicted adult height 2, and mid-parental height in early puberty gonadotropin-releasing hormone analog treated group; n = 50. *Difference between predicted adult height 2 and predicted adult height 1 (P < 0.001). #Difference between predicted adult height 2 and mid-parental height (P = 0.056)

Discussion

The present study showed that GnRHa treatment in EP girls for a period of about 2.5 years significantly ($P < 0.001$) increased the PAH at the end of the study when compared with the PAH at the beginning of the study; by the end of the study, PAH was not significantly different with the target height in this group. Although GnRHa treatment in EP girls does not increase the PAH compared with the

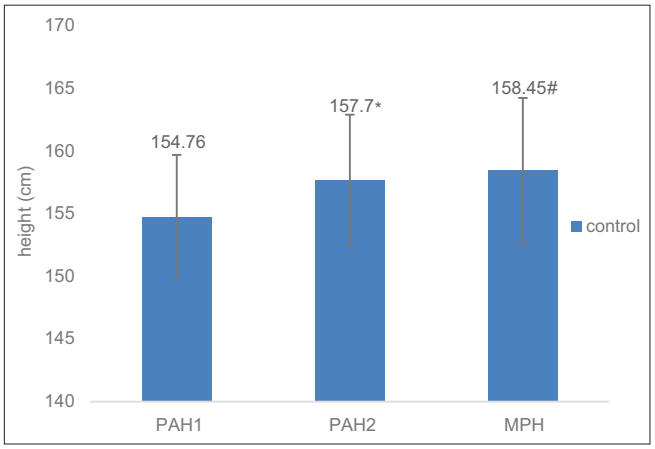

Figure 2: Predicted adult height 1, predicted adult height 2, and mid-parental height in early puberty control group; n = 33. *Difference between predicted adult height 2 and predicted adult height 1 (P<0.001). #Difference between predicted adult height 2 and mid-parental height (P = 0.029)

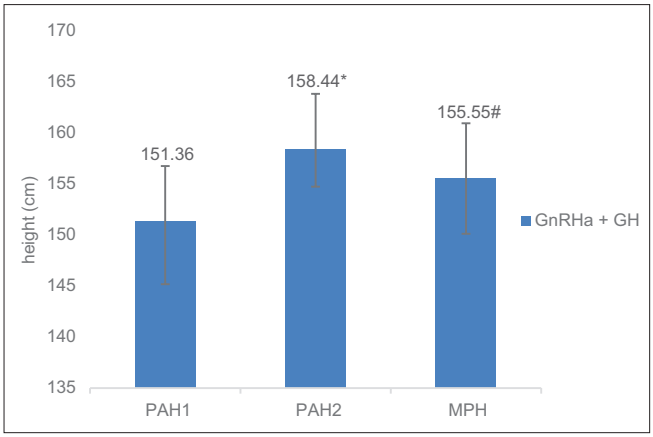

Figure 3: Predicted adult height 1, predicted adult height 2, and mid-parental height in early puberty gonadotropin-releasing hormone analog and recombinant human growth hormone-treated group; *n* = 45. *Difference between predicted adult height 2 and predicted adult height 1 (*P* < 0.001). #Difference between predicted adult height 2 and mid-parental height (*P* = 0.035)

control group, this treatment helps the treated girls to reach their target height in a longer time [Table 1 and Figure 1].

In the control group, although the PAH at the end of the study increased when compared with the beginning of the study, these girls could not attain their target height and their PAH was significantly lower than the target height. It may be concluded that treatment with GnRHa although could not increase the height of treated girls in comparison with the control group, it was slightly effective on the catch-up target height of treated girls, although insignificant.

In the report of Demirkale *et al*., treatment with GnRHa compensated the decreased PAH and normalized it, although the final height was not different with untreated girls.[12] This finding is in part in line with our study in EP girls treated with GnRHa. Some reports demonstrated that GnRHa treatment does not affect the final height in borderline EP or physiological normal puberty with rapid progress[13,14] which is in favor of our result. Bertelloni *et al*. in a meta-analysis with 483 cases of EP girls concluded that GnRHa treatment cannot widely change growth outcome and EP girls spontaneously attain their mid-parental height (MPH).[8] They concluded that GnRHa treatment cannot change the growth outcome of both treated and untreated EP girls and both groups have a similar final height which is compatible with MPH. Although GnRHa is the drug of choice in the treatment of CPP girls, the effectiveness of this treatment on improving height in EP girls is controversial.[15]

Treatment of EP girls with GnRHa for 0.9 ± 0.1 years shows that the adult height of treated group was not significantly different from the untreated control group; both groups had similar MPH and the height outcome was similar for both groups.[7] This report is also in line with our finding in the present study. EP girls in our study reach their MPH, but

Table 2: Clinical characteristics in girls treated with combination of gonadotropin-releasing hormone analogue and recombinant human growth hormone in comparison to control

Clinical characteristics	GnRHa plus rhGH	Controls	*P*
Age (years)	9.84±0.57	9.66±0.74	NS
Height (cm)	133.13±7.94	140.9±9.11	<0.001
Height SDS	−0.66±1	0.62±1.2	<0.001
Weight (kg)	32.23±6.66	37.11±8.45	0.006
BMI (kg/m^2)	18.10±2.17	18.61±3.19	NS
Bone age (years)	10.14±1.02	10.02±0.96	NS
Target height (cm)	155.55±5.42	158.45±5.80	NS
PAH_1 (cm)	151.36±6.17	154.76±5.14	NS
PAH_2 (cm)[a]	158.44±3.55	157.70±5.38	0.005

[a]By regression (co-variance) analysis and removing the conflicting variables (*P*=0.005). Target height is equal to mid parental height. *n*=33 in control group, *n*=45 in GnRHa plus rhGH-treated group. NS: Nonsignificant difference (*P*>0.05), BMI: Body mass index, PAH: Predicted adult height, PAH_1: PAH at the start of the study, PAH_2: PAH at the end of the study, rhGH: Recombinant human growth hormone, GnRHa: Gonadotropin-releasing hormone analogue, SDS: Standard deviation score

Table 3: Clinical characteristics in girls treated with combination of gonadotropin-releasing hormone analog and recombinant human growth hormone in comparison to girls treated with gonadotropin-releasing hormone analog alone

Clinical characteristics	GnRHa plus rhGH	GnRHa-treated girls	*P*
Age (years)	9.84±0.57	9.22±0.56	<0.001
Height (cm)	133.13±7.94	132.20±5.14	NS
Height SDS	−0.66±1	−0.3±0.7	NS
Weight (kg)	32.23±6.66	32.67±5.49	NS
BMI (kg/m^2)	18.10±2.17	18.64±2.39	NS
Bone age (years)	10.14±1.02	9.74±0.59	0.03
Target height (cm)	155.55±5.42	157.56±4.42	NS
PAH_1 (cm)	151.36±6.17	153.44±5.24	NS
PAH_2 (cm)[a]	158.44±3.55	157.50±3.41	0.008

[a]By regression (covariance) analysis and removing the conflicting variables (*P*=0.008). Target height is equal to mid-parental height. *n*=50 in GnRHa-treated group, *n*=45 in GnRHa plus rhGH-treated group. NS: Nonsignificant difference (*P*>0.05), BMI: Body mass index. PAH: Predicted adult height, PAH_1: PAH at the start of the study, PAH_2: PAH at the end of the study, rhGH: Recombinant human growth hormone, GnRHa: Gonadotropin-releasing hormone analog, SDS: Standard deviation score

untreated girls did not reach their MPH (*P* = 0.029); this result demonstrates that although GnRHa treatment did not significantly improve the height of EP girls in comparison with untreated group, it may help treated group to reach their target height.

The main finding of our study is that combined therapy with GnRHa and rhGH for about 2.5 years increased the PAH in this group [Tables 2, 3 and Figure 3]. The PAH with combined therapy is significantly higher than the

PAH in the control group (P = 0.005) at the end of the study. The PAH in EP girls treated with the combination of GnRHa and rhGH is also higher than the target height in this group; this finding is again in favor of the effective role for the combined therapy in catch up of the height in treated girls.

Retarded GnRH analogs can impair GnRH pulses and inhibit its action on pituitary and therefore inhibits gonadal hormones, leading to retarded or delay in BA and development of secondary sexual characteristics.

Growth hormone is also used to act at the epiphyseal growth plate accelerating the growth of long bones and subsequently improve the final height in treated girls.

As Table 2 shows the PAH at the end of the treatment with the combination of GnRHa and rhGH which is significantly higher than the control group at the end of treatment (P = 0.005) and PAH in the treated group which is also significantly higher than the target height in this group (P = 0.035). PAH in combined treated group at the end of the study is also significantly higher than the GnRHa treated group (P = 0.008). Karamizadeh *et al*. reported that in healthy adolescent girls with short stature who entered puberty at a normal age, combination therapy with GnRHa and rhGH increased the PAH at the end of the study against PAH at the start of the study by 4.13 ± 0.9 cm.[16] This report is in line with our result in the present study. Several studies have reported the effectiveness of GnRHa and rhGH combined therapy on the final height in CPP girls.[4,9,17,18] Song *et al*. in a meta-analysis from five studies of EP girls concluded that combination therapy could not significantly differ between final adult height SDS and initial height SDS in treated EP girls. Although individual reports suggest the beneficial effects of combined therapy on improving adult height[5] again, the controversies of view exist between experts in this field toward combined therapy, especially when the cost of drugs is too high. There is a report from China on GnRHa and rhGH in combination or GnRHa alone on the treatment of EP girls which argue that PAH at the end of combined therapy was higher than GnRHa alone, although the different was insignificant and both treatments had a similar effect on the final height of EP girls.[19] Our result in the present study is in line with those reports that showed combined therapy had more effect on the final height on EP girls than the GnRHa alone.

Conclusion

Accordance with our results, GnRHa therapy has a benefit effect in achievement of target height. Combination therapy with GnRHa plus rhGH increased their PAH more than both untreated and GnRHa groups.

Acknowledgments

This cohort study was part of a pediatric resident student thesis approved in Mashhad University of Medical Sciences.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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