IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

The Relationship of Gonadotropin-releasing Hormone Agonists and Anthropometric Indices of Girls with Premature Idiopathic Central Precocious Puberty: A Cohort Study

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ABSTRACT

Background: This study aims to determine the effect of different GnRH agonist brands on body mass index (BMI), weight, and height in patients referred to the pediatric endocrinology clinic of Akbar Hospital.

Methods: In this cohort study, 80 girls aged 5-8 years diagnosed with precocious puberty cases were included according to the Tanner staging and at the second puberty stage. The patients were classified into three groups of GnRH agonists, A, B, and C, receiving Diphereline, Microrelin, and Variopeptyl, respectively. Height, weight, and BMI were calculated every three months.

Results: In group A, the weight (P=0.007) and BMI (P<0.001) percentiles and weight (P=0.024) and height (P=0.021) Z-scores were significantly increased compared to the baseline. In group B, the weight (P=0.024) and height (P=0.020) Z-scores also increased at the end of the study. However, the changes in group C were not significant. In addition, the weight, height, and BMI Z-scores were significantly increased in normal-weight subjects compared to overweight and obese participants. The results of comparing the changes in the weight and height between the three-drug groups showed no significant difference (P=0.142 and 0.161, respectively).

Conclusion: The findings of this study revealed that GnRH agonists could increase height, weight, and BMI; however, this increase was not significant for one type of GnRH agonist. Future prospective long-term follow-up studies are required to elucidate whether GnRH treatment affects final adult weight and height and clarify the difference between various types of GnRH agonists among participants with diverse health statuses.

Keywords: Body mass index, GnRH agonist, Obesity, Precocious puberty

Introduction

Puberty is a complex biological process of sexual development, controlled by the activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion of the hypothalamus, which

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Please cite this paper as:
Badpeyma M, Molani-Gol R, Sistanian F, Khadem-Rezaiyan M, Eshraghi P, Samaei F, Faghfouri AH, Vakili R. The Relationship of Gonadotropin-releasing Hormone Agonists and Anthropometric Indices of Girls with Premature Idiopathic Central Precocious Puberty: A Cohort Study. Iranian Journal of Neonatology. 2024 Oct: 15(4). DOI: 10.22038/ijn.2024.74125.2433

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leads to the stimulation of hormonal cascade and gonadal activation (1). Pubertal timing is influenced by interactions among various genetic, environmental, nutritional, and socioeconomic factors. However, the ultimate mechanisms underlying the enhancement in pulsatile GnRH secretion at puberty have yet to be fully elucidated (2). Central precocious puberty (CPP) results from the premature activation of the hypothalamus-pituitary-ovarian axis. In girls, it is defined as the onset of secondary sexual development before age 8 with further progression, accompanied by increased growth velocity and bone age acceleration, usually leading to adult height impairment (2). CPP has an estimated overall prevalence of approximately 1 per 5000-10,000 children, with a five- to 10-fold higher incidence in girls than in boys (3-5). CPP is associated with potential sexual abuse, lower final adult height (FAH), increased risk of psychological disturbances, and increased risk of developing reproductive tract cancers and cardiovascular diseases (6, 7).

GnRH agonist (GnRHa) treatment for CPP has been considered a gold standard since early 1980(8), which down-regulates and desensitizes pituitary GnRH receptors, inhibiting the HPG axis, thereby slowing the onset of puberty (8, 9). Triptorelin acetate (TA) is commonly used in medical practice as a GnRHa. This therapy effectively desensitizes gonadotropic cells of the pituitary gland to GnRH by down-regulating the GnRH receptors; thus, pubertal development symptoms suppress or regress, and the acceleration of growth and bone maturation decreases (10, 11).

Despite the benefit and confirmed safety of GnRHa, concerns have been raised about the effect on body mass index (BMI) during and after GnRHa treatment in children with CPP. BMI increase during childhood and adolescence is linked to increased adult cardiometabolic risk (12, 13). As a result, monitoring changes in BMI during GnRHa treatment is critical; in most studies, there was no significant difference in BMI duration treatment (14-17). While other studies discovered that GnRHa therapy increased BMI, the observed relationship remains controversial (18-20). Some of the studies showed that attained height was not significantly different between treated and untreated groups (21, 22). On the other hand, few studies assessed different brands of this drug. Therefore, this study aimed to evaluate BMI, weight, and height changes in girls diagnosed with CPP before and after GnRHa therapy with different drug brands (Diphereline, Microrelin, and Variopeptyl) for at least 20 months.

Methods

Subjects

This prospective cohort study was performed among 80 girls diagnosed with idiopathic CPP referred to the Akbar Hospital's and Mashhad's endocrinology clinics during 2019-2020. The prevalence of central precocious puberty is higher in girls than in boys, and most of them are idiopathic CPP, while in boys, it is more due to accidents and brain lesions. The sample size concerning the study of Yang et al. (23), and using the formula of comparing a quantitative trait in the two groups, considering a 95% confidence level, a power of 80%, and a dropout rate error of 20%, was calculated to be 80 subjects. The patients were classified as GnRH agonists, Group A, B, and C, receiving Diphereline, Microrelin, and Variopeptyl. GnRHa brands are chosen according to the patient's preferences. They received 3.75 mg intramuscular GnRH (including Viphereline (IPSEN, France), Microrelin (Pooyesh Darou, Iran), and Variopeptyl (Varian Pharmed, Iran)) once a month or every three months during at least six months of treatment at the pediatric endocrinology clinic of Akbar Hospital, Mashhad, Iran. The researcher provided nutritional recommendations to all patients on a routine basis as part of the management during the study. The inclusion criteria for the diagnosis of CPP were an age of 5-8 years, diagnosed with precocious puberty by a pediatric endocrinologist (precocious puberty was diagnosed based on clinical findings, bone age determined by the same investigators using an X-ray of the left hand, according to the method of Greulich and Pyle (24), Ultrasound of the Uterine and ovarian, and patients less than eight years old with symptoms of secondary sexual characteristics (entrance stage II according to Tanner classification) were considered as precocious puberty], treatment with GnRHa in cases of progressive precocious puberty, progressive Tanner stage at the first visit, advanced bone age (short height at the time of onset puberty) and the onset of puberty at the age of less than six years).

Patients with a history of developmental disorders, familial short stature, long-term use of drugs with a toxic effect on the liver (such as glucocorticoids and anti-seizure), suffering from progressive systemic diseases of the central

nervous system and gonad suffering from thyroid disease, any sensitivity to GnRH agonists, suffering from chronic liver and kidney diseases, brain injuries, brain tumors, hydrocephaly, parents' lack of consent to participate in the study, and the presence of any conditions that cause changes in body composition [such as growth hormone reduction, congenital adrenal hyperplasia, or primary hypothyroidism] were excluded.

Data collection

Demographic, anthropometric, and radiological data (i.e., age, height, weight, pubertal status, CA, and BA) were collected on the first day of the GnRHa treatment. Patients were treated for an average of 20 months. They received one of the drugs, Diphereline, Microrelin, and Variopeptyl (at a dose of 3.75 mg), based on their economic status and the drug available on the market. Clinical and laboratory assessments were performed every three months, and height, weight, BMI, pubertal status, and bone age were measured and recorded. Pubertal stages were determined according to Marshall and Tanner (25). Height was measured using the Harpenden Stadiometer (Holtain Ltd., Crosswell, UK) with an accuracy of 0.1 centimeters, and body weight was measured to the nearest 0.1 kg using a digital scale (Dong-Sahn Jenix, Seoul, Korea). The BMI of each patient was calculated as weight divided by the square of height (kg/m2). The height, weight, and BMI Z-scores were calculated using the CDC Growth Charts (2). Also, based on baseline BMI, the patients with BMI percentiles<85th, the 85th–94th percentiles, and the ≥95th percentile were allocated to the normal weight, overweight and obese groups, respectively (3).

A single pediatric endocrinologist evaluated sexual maturity rating using the Tanner staging system. BA was estimated according to the method of Greulich and Pyle, based on an X-By the ultrasound results, uterine and ovarian volumes were more than 1.5 cc, ovarian and uterine sizes more than 20 mm and 35 mm, respectively, based on the pediatrician's opinion. The patients were classified into three GnRH agonist groups (Diphereline, Microrelin, and Variopeptyl).

Statistical Analysis

All the statistical analyses were performed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA). Percentages report the categorical values and the continuous data are expressed by mean ± standard deviation (SD). The one-way analysis of variance (ANOVA) with the linearity test was used to compare the means between the groups. The repeated measures of ANOVA were used to assess the changing trend in three-drug groups. The independent T-test with a confidence interval of 95% was employed to compare the quantitative value of both groups before and after intervention with each other. A P-value < 0.05 was considered statistically significant.

Ethical approval

The study was performed after the Medical Ethics Committee of the Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1398.213) examined any possible ethical issues. The patient's parents provided informed consent.

Results

The study population included 80 girls with CPP. Patients' mean CA and BA at the beginning of GnRHa treatment were 7.75± 1.08 and 8.75± 1.38 years, respectively. The BA was 1± years more than the CA at the beginning of GnRHa treatment. The mean duration of GnRHa treatment was 21.68 ± 12.66 months. The ratio of obesity and overweight in all patients was 7.4% and 25.9%, respectively. Of them, 57 were in group A, 10 in group B, and 13 in group C. As shown in Table 1, there is no significant difference between patients' anthropometric indices at the initiation of treatment in the three groups.

Changes in percentile and Z-score of weight, height, and BMI at the baseline and end of treatment between the three-drug groups are shown in Table 2. There was a significant difference in weight Z-score (P=0.024), weight percentile (P=0.007), height Z-score (P=0.021), and BMI percentile (P=<0.001) between baseline and end of Diphereline treatment. In group A, post-treatment weight Z-score (P=0.027) and height Z-score (P=0.020) significantly increased compared with the baseline. Although height, weight, and BMI increased in group C, these increases were not statistically significant.

Table 1. Baseline anthropometric data of participants (Mean ± SD).

Variables	Group A (N=57)	Group B (N=10)	Group C (N=13)	P-value*
Weight (kg)	28.11±8.09	24.22±2.09	25.89±4.20	0.245
Height (cm)	128.09±8.76	125.36±32.00	126.09±6.64	0.907
BMI	28.11±8.09	24.22±2.09	25.89±4.02	0.212

*One-way ANOVA test, P-value<0.05 is significant.
Group A, B, and C received Diphereline, Microrelin, and Variopeptyl, respectively.

Table 2. Changes in percentile and Z-score of weight, height, and BMI compared to the baseline of treatment between three groups

Variables	Group A					Group B					Group C				
	Baseline	Post-Treatment	DF	SD	P-value*	Baseline	Post-Treatment	DF	SD	P-value	Baseline	Post-Treatment	DF	SD	P-value
Weight percentile	26.15±69.64	25.89±75.97	6.33	13.48	0.007	24.62±56.25	22.70±63.25	7.00	4.69	0.058	59.00±18.50	57.00±21.52	-2.00	13.78	0.657
Weight Z-score	1.18±0.86	1.11±1.05	0.19	0.50	0.024	0.81±0.26	0.87±0.50	0.24	0.11	0.027	0.26±0.51	0.24±0.66	-0.02	0.41	0.842
Height percentile	24.77±66.47	25.12±68.33	1.86	11.39	0.223	15.96±33.27	24.95±37.78	4.51	14.73	0.358	56.23±19.87	60.76±19.23	4.53	9.23	0.102
Height Z-score	0.87±0.56	0.92±0.68	0.12	0.35	0.021	-0.52±0.48	-0.69±0.27	0.21	0.24	0.020	0.20±0.56	0.32±0.56	0.12	0.26	0.109
BMI percentile	26.15±62.39	26.05±73.14	10.75	20.16	<0.001	21.16±51.50	21.44±61.30	9.80	27.36	0.287	56.92±26.15	53.69±27.32	-3.23	16.65	0.498
BMI Z-score	0.98±0.88	7.81±1.56	0.68	7.79	0.513	0.82±0.14	-5.90±1.34	-1.48	5.96	0.450	0.29±0.87	0.20±0.90	-0.09	0.49	0.568

*Paired sample T-test, P<0.05 is significant. DF; Different.
Group A, B, and C received Diphereline, Microrelin, and Variopeptyl, respectively.

Table 3 shows the changes in the Z-score of weight, height, and BMI among normal-weight, overweight, and obese participants. In normal-weight subjects, the Z-score of weight, height, and BMI were significantly increased (P=0.006, 0.014, and <0.0001, respectively).

Table 4 compares the Z-scores of weight, height, and BMI changes in normal weight, overweight, and obese subjects among the three groups (A, B, and C). There was a significant difference in BMI Z-score changes among the normal-weight participants in the three groups, which decreased by 0.11 in group A and 0.04 in group C and increased by 0.26 in group B (P=0.03).

Figure 1 shows the trend of height Z-score changes between the three groups at six visits. The repeated measure ANOVA test results showed that the height difference Z-score changes between the three drugs at six visits were insignificant (P=0.648). However, there is an ascending trend during the six-visit period. As presented in Figure 2, there is no significant difference between the trend of weight Z-score changes at six visits between the three groups (P=0.422).

Table 3. Changes in percentile and Z-score of weight, height, and BMI within normal weight, overweight, and obese participants.

Mean	Normal weight	P-value*	Overweight	P-value	Obese	P-value
Weight z-score	0.20±0.44	0.006	0.26±0.37	0.089	-0.26±0.42	0.184
Height z-score	0.11±0.35	0.014	0.20±0.24	0.022	0.10±0.29	0.371
BMI z-score	0.35±0.71	<0.0001	0.07±0.43	0.584	-0.15±0.34	0.293

*One-way ANOVA test, P-value<0.05 is significant.

Table 4. Comparison of Z-score weight, height, and BMI changes in normal weight, overweight, and obese subjects among the three (A, B, and C) groups

Mean difference		Group C	Group B	Group A	P-value*
Normal weight	Weight Z-score	0.00±0.03	0.00±0.32	-0.30±0.48	0.146
	Height Z-score	0.20±0.08	0.15±0.11	0.35±0.13	0.846
	BMI Z-score	-0.00±0.04	0.25±0.26	-0.45±0.11	0.030
Overweight	Weight Z-score	0.00±0.51	0.00±0.00	0.38±0.22	0.520
	Height Z-score	0.00±0.48	0.00±0.41	0.22±0.13	0.259
	BMI Z-score	0.00±0.288	-0.00±0.51	0.43±0.11	0.389
Obese	Weight Z-score	0.00±0.03	0.00±0.32	-0.30±0.48	0.520
	Height Z-score	-0.00±0.08	0.29±0.50	-0.06±0.04	0.259
	BMI Z-score	0.38±0.004	-0.00±0.004	0.25±0.26	0.389

*One-way ANOVA test, P-value<0.05 is significant.
Group A, B, and C received Diphereline, Microrelin, and Variopeptyl, respectively.

Discussion

GnRHa treatment has been a standard of care in progressive EP for nearly four decades (8), and it has been shown that GnRHa is effective in treating patients with CPP (26). In this study, we investigated the effects of GnRH agonist therapy (including Diphereline, Microrelin, and Variopeptyl) on anthropometric indices in girls with idiopathic CPP to determine whether these (Microrelin and Variopeptyl) had similar effects compared with the commonly used medications such as Diphereline.

In the current study, in patients treated with Dipherelin and Microrelin, weight and height Z-

scores showed a significant increase; however, this increase was not significant in girls treated with Variopeptyl. Many other studies reported similar findings. Yang et al. show that the changes in BMI-standard deviation score during treatment significantly differed according to baseline BMI status (23). Similarly, Yoon et al. (27) reported a remarkable increase in BMI Z-score. BMI is one of the most studied factors in evaluating the effects of GnRHa treatment. Several other studies also demonstrated increased BMI during or following GnRHa treatment in subjects with CPP and early puberty (20, 28, 29). Nevertheless, some studies showed that GnRHa treatment did not affect BMI (15, 17, 30). One possible explanation for the increasing prevalence of obesity after GnRHa treatment may be related to increased leptin and insulin concentrations in overweight patients, which could be caused by converting adrenal androgen to estrogen because of aromatase activation in the adipose tissue (31).

The results of the effects of three drugs on Z-score changes of weight, height, and BMI among normal weight, overweight, and obese patients showed that change in BMI Z-score was significantly different only among normal-weight participants. In line with our findings, Wolter et al. (32) monitored the BMI Z-score of patients with CPP and detected a clear increase in BMI Z-score for the normal weight group during treatment but no change for the overweight/obese group. Park and Kim (33) also reported a significant increase in BMI Z-score during treatment, with no change in the overweight/obese group. Two other studies that reported an increase in BMI-standard deviation score in both groups showed that the change in BMI-standard deviation score was significantly greater in normal-weight patients than in overweight patients (28, 29); these findings are in accordance with our results. Patients' weight status may affect the effects of GnRHa on girls' weight with early puberty. Studies have shown that growth velocity in some patients during GnRHa treatment falls below the normal limit. Growth gradually decreases to the pre-pubertal rate during the first or second year of the treatment, and sometimes further deceleration occurs in the following years (34). children with obesity appear to be sexually developing earlier than lean children (35).

Furthermore, GnRHa inhibits sex steroid hormone secretion, which could suppress the development of obesity among overweight and obese patients (36). At the initiation of the treatment, more than 33% of our patients were obese and overweight. Recent studies reported that the proportion of obesity among patients with early puberty is approximately 20-25% (14-16). Therefore, unlike the overweight and obese patients who maintained a relatively stable body composition, the girls with normal weight at baseline showed a significant increase in the Z-score of weight, height, and BMI during the treatment period, which was mainly attributable to the difference in stature growth between them (23). Thus, weight control during early GnRHa treatment appears critical to preventing the development of obesity among girls with CPP.

Our study demonstrates that Microrelin and Variopeptyl affect body weight and BMI similarly to Diphereline. Each drug group's BMI and growth velocity change were similar during treatment. There are rare randomized trials that directly compared these three treatments in girls with CPP but appear similarly effective in suppressing the HPG axis. However, based on the obtained findings, Variopeptyl had no significant effects on increasing the Z-score of weight, height, and BMI, which can be helpful options. Recent consortium guidelines for using GnRHa in children recommended that conducting prospective studies is necessary to establish differences in efficacy among available GnRHa and current therapeutic regimens. Our study has some limitations, such as the lack of a control group because most CPP children underwent GnRHa treatment and differences in population age. Also, we did not include both sexes in the study and only studied girls; hence, our findings could not be applied to the general CPP population. We were unable to assess the economic status because it was difficult to use various tools to measure it. We recommended investigating economic status in future studies. However, this study has some strengths, such as relatively high study duration and assessing different brands of GnRH agonists.

Conclusion

The present study's findings revealed that three GnRH agonists, including Dipherelin, Microrelin, and Variopeptyl, can increase height, weight, and BMI; however, this increase was not significant in girls treated with Variopeptyl. Moreover, we found that the difference between the three-drug groups in weight and height change was significant in normal-weight individuals. Future prospective long-term follow-up studies are required to elucidate

whether GnRHa treatment affects final adult weight and height and to clarify the difference between various types of GnRH agonists in increasing weight and height among participants with diverse health statuses.

Acknowledgments

We appreciate the participants and their families. The trial was funded by the Mashhad University of Medical Sciences with grant number 970847.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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