Comparison of short-term efficacy between 1-month and 3-month depot gonadotropin-releasing hormone agonist in girls with central precocious puberty

**Running title:** Comparison between 1-month and 3-month depot GnRH agonists in CPP

Min Jin Jeon, MD¹, Jae Won Choe, MD², Hye Rim Chung, MD, PhD², Jae Hyun Kim, MD PhD²,³

¹Department of Pediatrics, Seoul National University Children’s Hospital, Seoul, Korea
²Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, Korea
³Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea

**Address for correspondence:** Jae Hyun Kim, MD, PhD

Department of Pediatrics, Seoul National University Bundang Hospital, 82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam 13620 Korea
Tel: +82-31-787-7287, Fax: +82-31-787-4054, Email: pedendo@snubh.org
Abstract

Purpose: Gonadotropin-releasing hormone agonist (GnRHa) has been the mainstay of central precocious puberty (CPP) treatment for decades, although there have been few reports comparing the efficacy between 1-month and 3-month depot GnRHa formulations. This study aimed to investigate the short-term efficacy of 1-month and 3-month depot GnRHa in girls with CPP.

Methods: Overall, 150 girls with CPP were included from a retrospective review of their medical records. Subjects in group 1 (n=105) were treated with 1-month depot GnRHa for ≥12 months and those in group 2 (n=45) with 1-month depot for 6 months and subsequent 3-month depot GnRHa for ≥6 months. Anthropometric and biochemical data were compared between groups at three time points (0, 6, and 12 months after GnRHa treatment).

Results: Demographic and clinical characteristics showed no difference between groups at baseline and 6 months after GnRHa treatment. After 12 months of GnRHa treatment, patients in both groups showed no difference in bone age (BA), chronological age (CA), BA-CA difference, height standard deviation score (SDS) for CA and BA, and body mass index SDS for CA and BA. The sexual maturity rate of the breast was prepubertal at 12 months in all subjects. GnRH-stimulated luteinizing hormone (LH) levels were suppressed during GnRHa treatment in both groups at 6 and 12 months, although LH levels in group 2 were higher than those in group 1.

Conclusion: Treatment with a 3-month depot GnRHa in CPP showed comparable short-term efficacy to the 1-month depot for anthropometric parameters and pubertal suppression.

Keywords: Precocious puberty, Gonadotropin-releasing hormone agonist, Treatment
outcome, Girls
Introduction

Central precocious puberty (CPP) is defined as the onset of breast development before 8 years in girls as a result of the premature activation of the hypothalamic-pituitary-gonadal axis. Early menarche can cause short adult stature because of early epiphyseal closure and emotional behavior and mood fluctuations because of physical differences with peers who have normal puberty. To prevent the adverse outcomes of CPP, early diagnosis and appropriate treatment is essential. After the biochemical confirmation of CPP using gonadotropin-releasing hormone (GnRH) stimulation tests in patients with early signs of puberty, depot formulation of GnRH agonists (GnRHa) is used as standard therapy.

Considering that continuous GnRH secretion, rather than intermittent exposure to the GnRH, suppresses pubertal development by desensitizing and downregulating the pituitary GnRH receptors, GnRHa is used to treat CPP. Several previous studies have reported that GnRH treatment in CPP regresses pubertal symptoms and signs and enhances the predicted adult height (PAH). In Korea, several doses of depot formulations of GnRHa including leuprolide (3.75 mg and 11.25 mg) and triptorelin (3.75 mg, 11.25 mg, and 22.5 mg) have been approved by the administrative agencies of Korean government for the treatment of CPP, although the most commonly used formulation of GnRHa is 1-month depot.

Previous reports have demonstrated that treatment of CPP with 3-month formulation efficiently suppresses pubertal development compared with 1-month formulation. Treatment with 3-month preparation might reduce the burden of injections and improve convenience and compliance. However, there are few reports that evaluate the effect of switching medication from 1-month to 3-month formulation. Additionally, there is currently no clinical information available on the 3-month GnRHa treatment in Korean patients with CPP. Therefore, this study aimed to compare the short-term efficacy of a 3-month depot
formulation of GnRHa with a 1-month depot in girls diagnosed with CPP with respect to anthropometric and laboratory parameters.

Materials and methods

1. Subjects

Girls who were diagnosed with CPP at the pediatric endocrinology clinic of the Seoul National University Bundang Hospital from January 2016 to December 2018 were considered as potential candidates for the present study. The inclusion criteria were as follows: (1) breast development before the age of 8 years, (2) advancement of bone age (BA) over chronological age (CA), (3) peak luteinizing hormone (LH) level ≥5 IU/L after GnRH stimulation test, (4) start of GnRHa treatment at the age of 7.0–8.9 years, and (5) GnRHa treatment using 1-month depot formulation for ≥12 months or 1-month depot formulation for 6 months and subsequently 3-month depot formulation for ≥6 months. Among the 264 subjects who met the inclusion criteria, a total of 150 girls with CPP were finally included in the present study, after the exclusion of subjects with the following characteristics: (1) subjects with CPP caused by organic brain lesions such as brain tumors and anomalies (n=11); (2) subjects with endocrinological disorders such as hypothyroidism, hyperthyroidism, or adrenal diseases (n=13); (3) subjects with chronic illness including diabetes mellitus or inflammatory disorders (n=30); or (4) subjects receiving recombinant human growth hormone (n=60).

This study was approved by the Seoul National University Bundang Hospital Institutional Review Board (IRB) (IRB number: B-2005-613-113), and the requirement for informed consent was waived by the IRB.
2. Methods

Data were obtained from a retrospective review of the medical records. Demographic and anthropometric data at the start, 6 months, and 12 months after GnRHa treatment were collected, including CA, BA, height, weight, body mass index (BMI), sexual maturity ratings (SMRs), midparental height, and birth weight. Height was measured using a Harpenden Stadiometer (Holtain Ltd., Crosswell, UK), and weight was measured using an electric balance (GL-310; G-Tech International Co. Ltd., Seoul, Korea). BMI was calculated with weight in kilograms divided by height in meters squared. Height and BMI were transformed into the standard deviation score (SDS) for corresponding CA and BA using the 2017 Korean National Growth Charts. BA from plain radiographs of the left hand was interpreted using the Greulich-Pyle method by a single pediatric endocrinologist. SMR was assessed using the Marshall and Tanner method. PAH was calculated according to the Bayley-Pinneau method.

All subjects underwent GnRH stimulation tests for the diagnosis of CPP. GnRH stimulation tests were performed using an intravenous injection of 0.1 mg of synthetic GnRH (Relefact; Sanofi-Aventis, Frankfurt, Germany), and blood samples for the measurement of LH, follicle-stimulating hormone (FSH), and estradiol were obtained before, 15, 30, 45, and 60 min after GnRH injection. Basal and peak levels of LH and FSH and basal estradiol levels were used for the analysis. LH and FSH levels were measured using immunoradiometric assays, and estradiol levels were measured via radioimmunoassay (DIAsource, Ottignies-Louvain-la-Neuve, Belgium).

Study subjects were divided into two groups according to the mode of GnRHa
administration (Fig. 1). Group 1 (n=105) comprised subjects treated with a 1-month depot formulation of GnRHa (leuprolide acetate; Leuplin® depot 3.75 mg, Takeda, Japan) every 4 weeks for at least 1 year. Group 2 (n=45) comprised subjects treated with 1-month depot formulation of GnRHa (leuprolide acetate; Leuplin® depot 3.75 mg, Takeda, Japan) every 4 weeks for the first 6 months and subsequently switched to 3-month depot formulation (leuprolide acetate; Leuplin® DPS depot 11.25 mg, Takeda, Japan) administered every 3 months for at least 6 months. Initially, 60–90 μg/kg of leuprolide acetate was administered subcutaneously every 4 weeks for all subjects. In group 2, the dose of the 3-month depot formulation was three times the last dose of the 1-month depot formulation. The dose of the 1-month or 3-month depot formulation was adjusted according to height velocity and SMR. Every 6 months, the LH level at 30 min after synthetic GnRH administration was measured. Stimulated LH levels of less than 3 IU/L were considered as sufficient pubertal suppression.16)

3. Statistical analyses

Data analysis was performed using Stata 16.1 (StataCorp LP, College Station, TX, USA). Data are presented as mean ± standard deviation for continuous variables and the number of subjects with percentage for categorical variables. Student’s t-test and Fisher’s exact test were used to compare groups 1 and 2. For comparison of continuous or categorical variables obtained at three time points in each group, repeated measures analysis of variance or Fisher’s exact test was used, respectively. A P value less than 0.05 was considered statistically significant.
Results

1. Baseline characteristics of the study subjects

The baseline characteristics of the 150 patients enrolled in this study are presented in Table 1. The mean CA and BA and the difference between BA and CA were 8.4 ± 0.6 years, 10.0 ± 0.7 years, and 1.6 ± 0.7 years, respectively, which revealed no difference in both groups (all P>0.05). Furthermore, there were no significant differences in height SDS for CA and BA, BMI SDS for CA and BA, and PAH. Although breast SMR was higher in group 2 than that in group 1 (P<0.001), there was no difference between basal and peak LH and FSH and basal estradiol levels between the two groups. Dose of GnRHa in group 2 was significantly higher than that in group 1 (84.9 ± 9.0 vs. 78.4 ± 9.3 μg/kg/mo, P<0.001).

2. Changes in clinical parameters during GnRHa treatment

During the treatment, subjects in both groups showed a significant decrease in BA-CA difference and height SDS for CA and a significant increase in height SDS for BA, BMI SDS for CA and BA, and PAH (Table 2 and Fig. 2). Breast SMR also significantly regressed in both groups. Among participants, 6.7% at 6 months and 4.7% at 12 months after GnRHa treatment showed breast SMR 2, although there was no significant difference between groups. LH levels after GnRH stimulation suppressed at 6 months and sustained at 12 months in both groups (1.1 ± 0.5 IU/L at 6 months and 1.1 ± 0.4 IU/L at 12 months in group 1 and 1.2 ± 1.0 IU/L at 6 months and 1.4 ± 0.5 IU/L at 12 months in group 2). At 6 months, two patients in group 2 were not suppressed biochemically, although all patients showed LH levels <3 IU/L at 1 year.
3. Comparison between groups at 6 months and 1 year after GnRHa treatment

There was no significant difference in CA, BA, BA-CA difference, height SDS for BA and CA, BMI SDS for BA and CA, PAH, and PAH SDS between groups at 6 and 12 months after GnRHa treatment (Table 2 and Fig. 2). LH level after GnRH stimulation in group 2 was significantly higher than that in group 1 (1.1 ± 0.4 IU/L vs. 1.4 ± 0.5 IU/L, \(P<0.001\)) after 12 months of treatment, although LH levels were adequately suppressed in all subjects. The dose of GnRHa (\(\mu g/kg/mo\)) was not significantly different between groups at 6 and 12 months after GnRHa treatment. In both groups, breast SMR was sufficiently suppressed (Table 2).

Discussion

Long-acting GnRHas have been the standard treatment for CPP since the mid-1980s.\(^2\) In the present study, we compared the efficacy of a 3-month depot formulation of GnRHa with a 1-month depot in girls with CPP. For the 6-month period of comparison between 1-month and 3-month GnRHa treatment, anthropometric, radiographic, and laboratory parameters showed no difference between groups, which provided comparable short-term efficacy of 3-month depot GnRHa formulation to 1-month depot. Although LH level after GnRH stimulation was higher in group 2 than that in group 1 at 12 months, LH levels were suppressed sufficiently in both groups.

Administration of GnRHa in CPP patients suppresses pubertal progression by desensitizing and downregulating pituitary GnRH receptors. In the present study, breast SMR was decreased at 6 and 12 months after GnRHa treatment in both groups. Moreover, GnRH-stimulated LH levels showed sufficient suppression of pubertal development regardless of
GnRHa formulations. In other studies using a 3-month depot formulation, similar results were demonstrated. Carel et al. observed that 3-month depot formulation of leuprolide acetate (11.25 mg) effectively suppressed gonadotropin secretion.\(^{17}\) A 36-month study showed that leuprolide acetate 3-month depot effectively suppressed pubertal symptoms and signs with no new adverse effects.\(^{18}\) Triptorelin 11.25 mg 3-month depot also effectively suppressed LH levels.\(^{19}\) Dose of GnRHa (μg/kg/mo) decreased during treatment period because of weight gain (Table 2). In this study, dose of GnRHa (mg/mo) had not changed when pubertal sign was sufficiently suppressed.

Several studies have shown that GnRHa treatment improves the final height for CPP patients.\(^{7, 20}\) Fuld et al. reported that GnRHa with 1-month 7.5 mg, 3-month 11.25 mg, and 3-month 22.5 mg showed effective suppression, and there was no significant difference in height, BA, and PAH in all groups.\(^{10}\) Bertelloni et al. showed similar adult height between girls treated with monthly (3.75 mg) vs. quarterly triptorelin (11.25 mg).\(^{21}\) The results of the present study were consistent with the those of previous studies. The height SDS for BA and PAH increased during treatment in both groups. Furthermore, BA-CA difference decreased during treatment, indicating the attenuation of BA advancement regardless of the type of GnRHa. Some studies showed that greater LH suppression increased the PAH.\(^{22, 23}\) In this study, after 12 months of treatment, although LH level was higher in 3-month depot than that in 1-month depot, PAH showed no statistically significant difference (160.2 ± 5.8 cm for group 1 and 159.8 ± 5.0 cm for group 2). Further long-term studies with leuprolide acetate are required to assess the final height.

There has been controversy regarding the association between GnRHa treatment and weight gain or obesity.\(^{24}\) Several studies showed increased BMI SDS during GnRHa treatment and decreased BMI SDS after discontinuation of GnRHa.\(^{25-28}\) In a study with 1-
month GnRHa depot formulation, the proportion of normal weight, overweight, and obesity was not significantly different in girls with CPP before and after the discontinuation of GnRHa treatment. Increase in BMI SDS during GnRHa treatment might be associated with relatively more gain of weight than height because of pubertal suppression by GnRHa. In this study, GnRHa treatment significantly increased BMI and BMI SDS in both groups over 1 year of GnRHa treatment, which was in concordance with previous studies. However, there was no significant difference in change of BMI SDS regardless of type of GnRHa. Additional long-term follow-up is required.

The doses of GnRHa administered in CPP vary worldwide. In the United States, the recommended starting doses of 1-month and 3-month depot leuprolide preparations range from 7.5 mg to 15 mg and 11.25 mg or 30 mg, respectively. On the contrary, Europe and Asia established a lower standard dose with 3.75 mg. Although the dose of GnRHa in CPP patients was less in Korea and Asia than that in other countries, low dose of GnRHa treatment efficiently suppressed the pituitary-gonadal axis, and PAH was not different from those treated with higher dose. After GnRHa treatment at 12 months in both groups, pubertal symptoms regressed and stabilized and LH levels were suppressed.

Our study has several limitations. First, this was a retrospective single-center study with a relatively short study duration. Second, the evaluation for the adverse events of 1-month and 3-month depot was not performed. However, all subjects in both groups tolerated each GnRHa well and continued to use at least 12 months. Nonetheless, this study is the first to compare the efficacy of 1-month and 3-month depot formulation of GnRHa in Korean patients with CPP.

In conclusion, the 3-month depot formulation of GnRHa effectively suppressed the pituitary-gonadal axis and gonadotropin secretion in girls with CPP. Treatment with a 3-
month depot GnRHa was comparable to a 1-month depot in terms of successful inhibition of pubertal progression, attenuation of BA advancement and increase in PAH after a safe switch from monthly formulation. Considering convenience and compliance, a 3-month depot formulation could be an alternative option for the treatment of CPP. Further long-term prospective studies are required to investigate its efficacy and safety profile.

**Conflicts of interest**

JHK received honorarium from Takeda, Ferring, and Ipsen. Except for that, no potential conflict of interest relevant to this article was reported.
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Figure legends

Fig. 1. Scheme of the present study.

Fig. 2. Changes in (A) height SDS for CA, (B) height SDS for BA, (C) BMI SDS for CA, and (D) BMI SDS for BA by groups and visits. SDS, standard deviation score; CA, chronological age; and BA, bone age.
Tables

Table 1. Baseline demographic and clinical characteristics of study subjects

| Variables               | Total (n= 150, 100%) | Group 1* (n = 105, 70%) | Group 2* (n = 45, 30%) | P value† |
|-------------------------|-----------------------|-------------------------|------------------------|----------|
| CA (yr)                 | 8.4 ± 0.6             | 8.4 ± 0.6               | 8.4 ± 0.6              | 0.621    |
| BA (yr)                 | 10.0 ± 0.7            | 10.0 ± 0.7              | 10.0 ± 0.6             | 0.935    |
| BA - CA (yr)            | 1.6 ± 0.7             | 1.6 ± 0.7               | 1.6 ± 0.5              | 0.701    |
| Height (cm)             | 132.0 ± 5.3           | 132.0 ± 5.2             | 132.0 ± 5.5            | 0.954    |
| Height SDS for CA       | 0.8 ± 0.8             | 0.8 ± 0.8               | 0.8 ± 0.8              | 0.767    |
| Height SDS for BA       | -1.2 ± 0.8            | -1.2 ± 0.8              | -1.3 ± 0.8             | 0.909    |
| PAH (cm)                | 158.5 ± 6.0           | 158.5 ± 6.2             | 158.5 ± 5.3            | 0.969    |
| PAH SDS                 | -0.5 ± 1.2            | -0.5 ± 1.3              | -0.5 ± 1.1             | 0.936    |
| BMI (kg/m²)             | 17.1 ± 1.8            | 17.2 ± 1.8              | 17.0 ± 2.0             | 0.676    |
| BMI SDS for CA          | 0.2 ± 0.8             | 0.2 ± 0.8               | 0.2 ± 0.8              | 0.612    |
| BMI SDS for BA          | -0.6 ± 0.7            | -0.5 ± 0.7              | -0.6 ± 0.7             | 0.548    |
| Midparental height (cm) | 159.8 ± 5.1           | 160.0 ± 3.8             | 159.5 ± 7.3            | 0.572    |
| Midparental height SDS  | -0.2 ± 1.1            | -0.2 ± 0.8              | -0.3 ± 1.7             | 0.470    |
| Small for gestational age, n (%) | 9 (6.0%) | 4 (3.8%) | 5 (11.1%) | 0.084 |
| Basal LH (IU/L)         | 0.9 ± 0.7             | 1.0 ± 0.7               | 0.9 ± 0.7              | 0.578    |
| Basal FSH (IU/L)        | 2.2 ± 1.3             | 2.2 ± 1.2               | 2.3 ± 1.4              | 0.493    |
| Peak LH (IU/L)          | 10.9 ± 7.0            | 11.2 ± 7.0              | 10.3 ± 7.0             | 0.463    |
| Peak FSH (IU/L)         | 11.3 ± 5.4            | 11.5 ± 5.4              | 11.1 ± 5.3             | 0.698    |
| Estradiol (pg/mL)       | 30.1 ± 16.6           | 31.5 ± 17.7             | 26.8 ± 13.4            | 0.110    |
| Dose of GnRH agonist (μg/kg/mo) | 82.9 ± 9.0 | 84.9 ± 8.2 | 78.4 ± 9.3 | <0.001 |
|---------------------------------|------------|------------|------------|--------|
| Breast SMR (I/II/III/IV/V)      | 0/94/55/1/0| 0/76/28/1/0| 0/18/27/0/0| <0.001 |

*Group 1 refers to subjects treated with 1-month depot formulation for 1 year and Group 2 with 1-month depot formulation for 6 months and subsequently switch to 3-month depot formulation.

†P value for comparison between Group 1 and Group 2.

Abbreviations: CA, chronological age; BA, bone age; SDS, standard deviation score; PAH, predicted adult height; BMI, body mass index; LH, luteinizing hormone; FSH, follicular stimulating hormone; GnRH, gonadotropin-releasing hormone; SMR, sexual maturity rate by Tanner stage.
Table 2. Comparison of clinical parameters between groups at 6 and 12 months by groups after GnRH agonist treatment

| Variables         | Group | Baseline     | 6 month      | 12 month     | P value† |
|-------------------|-------|--------------|--------------|--------------|----------|
| CA (yr)           | 1     | 8.4 ± 0.6    | 8.9 ± 0.7    | 9.4 ± 0.7    | <0.001   |
|                   | 2     | 8.4 ± 0.6    | 8.9 ± 0.6    | 9.4 ± 0.6    | <0.001   |
| BA (yr)           | 1     | 10.0 ± 0.7   | 10.4 ± 0.7   | 10.6 ± 0.6   | <0.001   |
|                   | 2     | 10.0 ± 0.6   | 10.4 ± 0.6   | 10.7 ± 0.5   | <0.001   |
| BA - CA (yr)      | 1     | 1.6 ± 0.7    | 1.5 ± 0.7    | 1.2 ± 0.7    | <0.001   |
|                   | 2     | 1.6 ± 0.5    | 1.5 ± 0.6    | 1.3 ± 0.6    | <0.001   |
| Height (cm)       | 1     | 132.0 ± 5.2  | 135.3 ± 5.3  | 137.8 ± 5.3  | <0.001   |
|                   | 2     | 132.0 ± 5.5  | 135.5 ± 5.4  | 138.1 ± 5.6  | <0.001   |
| Height SDS for CA | 1     | 0.8 ± 0.8    | 0.8 ± 0.8    | 0.7 ± 0.8    | <0.001   |
|                   | 2     | 0.8 ± 0.8    | 0.9 ± 0.8    | 0.8 ± 0.8    | 0.020    |
| Height SDS for BA | 1     | -1.2 ± 0.8   | -1.1 ± 0.8   | -0.9 ± 0.8   | <0.001   |
|                   | 2     | -1.3 ± 0.8   | -1.0 ± 0.7   | -0.9 ± 0.7   | <0.001   |
| PAH (cm)          | 1     | 158.5 ± 6.2  | 159.2 ± 6.0  | 160.2 ± 5.8  | <0.001   |
|                   | 2     | 158.5 ± 5.3  | 159.3 ± 5.3  | 159.8 ± 5.0  | 0.009    |
| PAH SDS           | 1     | -0.5 ± 1.3   | -0.3 ± 1.2   | -0.1 ± 1.2   | <0.001   |
|                   | 2     | -0.5 ± 1.1   | -0.3 ± 1.1   | -0.2 ± 1.0   | 0.008    |
| BMI (kg/m²)       | 1     | 17.2 ± 1.8   | 17.7 ± 1.9   | 18.3 ± 2.0   | <0.001   |
|                   | 2     | 17.0 ± 2.0   | 17.7 ± 2.0   | 18.3 ± 2.3   | <0.001   |
| BMI SDS for CA    | 1     | 0.2 ± 0.8    | 0.3 ± 0.8    | 0.4 ± 0.8    | <0.001   |
|                   | 2     | 0.2 ± 0.8    | 0.3 ± 0.7    | 0.4 ± 0.8    | <0.001   |
| Measurement                                    | Group 1 (n=105) | Group 2 (n=45) |
|-----------------------------------------------|-----------------|----------------|
| BMI SDS for BA                                |                 |                |
| 1                                            | -0.5 ± 0.7<sup>a,b</sup> | -0.4 ± 0.8<sup>a,c</sup> |
| 2                                            | -0.6 ± 0.7<sup>a,b</sup> | -0.3 ± 0.8<sup>b,c</sup> |
| LH after GnRH stimulation (IU/L)              |                 |                |
| 1                                            | 11.2 ± 7.0<sup>a,b</sup> | 1.1 ± 0.5<sup>a</sup> |
| 2                                            | 10.3 ± 7.0<sup>a,b</sup> | 1.2 ± 1.0<sup>a</sup> |
| Dose of GnRH agonist (μg/kg/mo)               |                 |                |
| 1                                            | 84.9 ± 8.2<sup>a,b,++</sup> | 79.0 ± 9.4<sup>a,c</sup> |
| 2                                            | 78.4 ± 9.3<sup>b,++</sup> | 76.8 ± 16.3<sup>c</sup> |
| Breast SMR (I/II/III/IV/V)                    |                 |                |
| 1                                            | 0/76/28/1/0<sup>++</sup> | 97/8/0/0/0 |
| 2                                            | 0/18/27/0/0<sup>++</sup> | 43/2/0/0/0 |

Group 1 (n=105) refers to subjects treated with 1-month depot formulation for 1 year and Group 2 (n=45) with 1-month depot formulation for 6 months and subsequently switch to 3-month depot formulation.

P value from repeated measures analysis of variance of baseline, 6 month and 12 month.

Superscript a, b, and c indicate P <0.05 between baseline and 6 month, between 0 and 12 month, and between 6 and 12 month, respectively. Superscript * and ** indicate P <0.05 and P<0.01 between Group 1 and 2, respectively.

Abbreviations: CA, chronological age; BA, bone age; SDS, standard deviation score; PAH, predicted adult height; BMI, body mass index; LH, luteinizing hormone; FSH, follicular stimulating hormone; GnRH, gonadotropin releasing hormone; SMR, sexual maturity rate by Tanner stage.
Figure 1.

Group 1 (n = 105)
Leuprolide 3.75 mg every 4 weeks

Group 2 (n = 45)
Leuprolide 11.25 mg every 3 months

0 mo 6 mo 12 mo
Fig. 2.

(A) Height SDS for CA over time.

- • 1-mo depot
- ■ 3-mo depot

Visit
0 month 6 month 12 month
Fig. 2.
Fig. 2.