

Original Article

Treatment with depot leuprolide acetate in girls with idiopathic precocious puberty: What is the best parameter to decide the initial dose?

Short Title: Initial dose of leuprolide acetate in girls with CPP

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Key words: central precocious puberty, leuprolide, GnRH, GnRH analogue, gonadotropin releasing hormone agonist, precocious puberty, puberty

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What is already known on this topic?

Insufficient suppression due to inadequate dose of GnRH analogues (GnRHa) in central precocious puberty (CPP) may result in continued advancement of bone limiting final height; whereas unnecessarily high doses may increase the risk of side effects, as well as total treatment costs. Monthly GnRHa injections are administered in different doses in different countries. For leuprolide acetate, lower doses (3.75 mg/28 days, 80–120 mcg/kg/28 days) are preferred in Europe and Asia, while higher doses (7.5–15 mg/28 days, 200–300 mcg/kg/28 days) are used in the United States of America.

What this study adds?

Leuprolide acetate treatment in doses of 3.75 mg/28 days is effective in suppressing hypothalamo-pituitary-gonadal (HPG) axis in majority of girls with idiopathic CPP. This treatment option is also more cost-effective than an initial high dose of 7.5 mg/28 days dose. Higher initial dose may be preferred in patients with a body weight ≥ 36 kg or BMI-SDS ≥ 1.6 for effective suppression of HPG axis.

Abstract

Background&objectives: Doses of GnRH analogues used to treat idiopathic central precocious puberty (iCPP) may vary with clinician preference. Aim of this study is to evaluate the efficacy of a monthly 3.75 mg dose of leuprolide acetate (LA) to suppress the hypothalamo-pituitary-gonadal (HPG) axis in girls with iCPP and to determine factors that may have an impact on the suppressing dose.

Materials&Methods: A total of 220 girls receiving LA for iCPP were included. LA is started at a dose of 3.75 mg/28 days, and suppression is examined using GnRH test at the 3rd month. Clinical signs and

symptoms of puberty were also evaluated to determine whether pubertal suppression was achieved clinically. Dose of LA is increased to 7.5mg/28 days in those who have a peak LH \geq 2IU/L and in whom adequate suppression of pubertal signs was not achieved. ROC curves were used to determine thresholds for clinical and hormonal factors with an impact on the suppressing dose of LA. We analyzed whether thresholds differentiate two populations using LA either at a dose of 3.75mg or 7.5mg, with logistic regression analyses.

Results: Peak stimulated LH in 88.6% of the patients was $<$ 2IU/L under treatment with 3.75 mg. Best threshold values that differentiate the two doses were 36.2kg for body weight (BW), 1.64 for BMI-SDS ($p < 0.001$). Multiple logistic regressions showed BW, and BMI-SDS above thresholds indicated requirement of LA at a dose of 7.5mg/28 days ($p < 0.001$).

Conclusion: 3.75 mg monthly injections of LA is an effective treatment in majority of girls with iCPP, however higher initial dose may be preferred in patients with a BW \geq 36kg or BMI-SDS \geq 1.6 for effective suppression of HPG axis.

Key words: central precocious puberty, leuprolide, GnRH, GnRH analogue, gonadotropin releasing hormone agonist, precocious puberty, puberty

Introduction

The aim of GnRH analogue (GnRHa) treatment in central precocious puberty (CPP) is to allow normal growth enabling a normal adult height and relieve psychosocial stress associated with early puberty (1-3). The intended long-term goals in such a treatment include suppression of bone advancement and attainment of an age appropriate growth rate, in order to achieve a normal adult height parallel to target height (1, 4). While short-acting nasal and daily injectable forms of GnRHa have been used previously, today, long-acting (monthly) or very-long-acting (three months) depot formulations or yearly implants that facilitate adherence to treatment are more commonly preferred (1, 3, 5).

Insufficient suppression due to inadequate dose of GnRHa may result in continued advancement of bone limiting final height; whereas unnecessarily high doses may increase the risk of side effects, as well as total treatment costs. Higher doses are shown to suppress both growth and bone mineral accrual rates (6, 7). The doses of GnRH analogues used in CPP may vary with clinician preference as well as local regulatory approvals. Monthly GnRHa injections are administered in different doses in different countries. For leuprolide acetate, lower doses (3.75mg/28 days, 80–120mcg/kg/28 days) are preferred in Europe and Asia (8-10), while higher doses (7.5-15 mg/28 days, 200–300 mcg/kg/28 days) are used in the United States of America (11). In the face of such great variation, best dose for optimal pituitary desensitization during monthly leuprolide treatment is still a matter of discussion. The aim of this study is to evaluate the efficacy of a monthly 3.75 mg dose of leuprolide acetate (LA) to suppress the hypothalamo-pituitary-gonadal (HPG) axis in girls with idiopathic CPP (iCPP) and to determine factors that may have an impact on the suppressing dose. We also aimed to define the best predictor among these factors for the optimal initial dose of LA.

Materials and Methods

A total of 220 girls followed with the diagnosis of iCPP between January 2012 and January 2018 who had received 3.75 mg LA (Lucrin depot, subcutaneous or intramuscular) once every 28 days were evaluated in the present study. Age at diagnosis, bone age, body weight, height, pubertal stage, basal estradiol levels, and basal and stimulated gonadotropin levels, pelvic ultrasonography and MRI findings of pituitary gland were recorded. CPP was diagnosed based on breast development being at Tanner stage 2 or higher before 8 years of age, and peak luteinizing hormone values \geq 5IU/L during GnRH test (12). GnRH test was performed in all patients at the diagnosis. Blood samples were collected at minute 0 for follicle stimulating hormone (FSH) and LH measurements, and then the patients were intravenously administered 100 μ g/m² of GnRH (gonadorelin acetate, Ferring®). Following drug administration, blood samples were collected at 20, 40, 60, and 120 min for FSH and LH measurement (13). Except for 4 patients presenting with menarche, all patients were followed for 3-6 months before the treatment decision. GnRHa treatment was given to the cases with progressive CPP who were determined according to the following criteria; a. Growth velocity above 6 cm/year, b. Advanced bone age (Bone age \geq 2 years above chronological age), c. Rapid progression in pubertal stages (Progression of puberty from one stage to another in less than 6 months), d. Loss in the predicted adult height compared to target height (14). Pituitary MRI was performed on all cases and the underlying organic pathology was investigated. Cases with no pathological MRI findings were

considered as idiopathic, and were included in the study. Subjects were excluded from the analysis if they had any additional conditions that might affect puberty onset (e.g. hypothyroidism, growth hormone deficiency, and congenital adrenal hyperplasia). LA is started at an initial dose of 3.75 mg/28 days to all patients with iCPP. For all the patients who started GnRHa treatment, GnRH test was repeated in the third month of treatment and the HPG axis was considered to be suppressed if peak LH levels were $<2\text{IU/L}$ (15-17). Clinical signs and symptoms of puberty were also evaluated to determine whether pubertal suppression was achieved clinically. Parameters of good clinical control included stabilization or regression of pubertal findings, decrease in height velocity to prepubertal levels, cessation of bone age progression, and improvement in final height prediction. The dose of LA is increased to 7.5 mg/28 days in those who have a peak LH $\geq 2\text{IU/L}$ and in whom clinical suppression of puberty was not achieved. All patients who had a peak LH $\geq 2\text{IU/L}$ in the 3rd month GnRH test did not have adequate clinical suppression of puberty and dose of LA was increased in all of these cases. Higher dose is similarly tested with GnRH test for appropriate suppression of HPG 3 months later. We compared clinical and hormonal characteristics of the two populations whose HPG axis was suppressed either with 3.75mg/28 days or 7.5mg/28 days of LA. Follow up included clinical and hormonal evaluations of all patients every 6 months after the initial treatment and during long-term follow-up, continuous clinical and hormonal suppression was observed.

Auxological parameters

Body weights were measured with a digital body weighing scale and heights were measured in the standing position with a Harpenden stadiometer by trained nurse on height measurements and auxology. The percentile curves of the Centers for Disease Control and Prevention(CDC) were used to interpret the growth data. Height standard deviation scores(SDS) for chronological age and bone age were calculated using CDC charts. The body mass index(BMI) was calculated using the formula weight in kg/height in meters squared. BMI-SDS were calculated according to the LMS method using CDC charts (18). Puberty staging was carried out using Marshall and Tanner staging (19). The bone age was evaluated using the Greulich and Pyle method from the bone age atlas (20).

Hormone assays

The immunochemiluminometric assay (ICMA) method using commercial kits (ARCHITECT System, Abbott Laboratory Diagnostics, USA) were used to measure FSH, LH and estradiol levels. The sensitivity of the FSH, LH, and estradiol assays was 0.3, 0.07 IU/l, and 10 pg/ml respectively.

Ethics

The study protocol was approved by Ethics Committee of Hacettepe University (Approval Number: GO 19/453-41). The requirement for informed consent was waived due to the retrospective nature of the study.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for Social Sciences software package for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). Testing for normality was performed by Shapiro-Wilk test. Data is shown as mean \pm standard deviation and student's t-test was used in comparisons of independent samples. ROC curves were used to determine threshold levels for the factors (age, body weight, BMI, BMI-SDS, basal LH, basal estradiol, peak stimulated LH) with an impact on the dose of LA that suppressed HPG axis. We analyzed whether these thresholds differentiate the two populations of patients whose HPG axis was suppressed either with 3.75 mg/28 days or 7.5 mg/28 days of LA using univariate logistic regression. Pubertal stages were grouped into early (Tanner 2&3) vs advanced (Tanner 4 &5), and impact of pubertal stages on suppressing doses of LA were also analyzed. The statistically significant factors in univariate analysis were reevaluated using multiple logistic regression analysis. A p value of less than 0.05 was considered statistically significant.

Results

Peak stimulated LH in 88.6% (195/220) of the patients was $<2\text{IU/L}$ at the 3rd month of treatment with LA at a dose of 3.75 mg/28 days. In the remaining 11.4% (25/220), the LA dose was increased to 7.5 mg/28 days, as puberty suppression was not achieved clinically and hormonally. GnRH test was repeated in patients who received 7.5mg/28 days at the 3rd month of dose escalation. The peak LH levels were found to be $<2\text{IU/L}$ in all patients, and hormonal puberty suppression was achieved in all of them. Regression in the clinical signs and symptoms of puberty and cessation in bone age progression were observed and growth rates decreased to prepubertal levels in all patients with

successful hormonal suppression. Consequently, suppression of HPG axis was achieved in all patients in the 6th month of treatment (Table 1).

Among cases that achieved HPG suppression at the dose of 3.75 mg LA/28 days, the pubertal stage at the time of diagnosis was Tanner stage 3 in 54.4% of cases (106/195), Tanner stage 2 in 35.9% (70/195) and Tanner stage 4 in 9.7% (19/195). Among the cases with successful suppression at the dose of 7.5 mg LA/28 days, 60% (15/25) were at Tanner stage 3, 24% (6/25) were at Tanner stage 4 and 16% (4/25) were at Tanner stage 5 at the time of diagnosis. These four patients who were at Tanner stage 5 at the time of diagnosis presented with menarche. There were no cases presenting with menarche among the patients whose puberty were suppressed with 3.75 mg LA. The stage of puberty at the time of diagnosis was significantly advanced among patients for whom the effective dose was 7.5 mg ($p < 0.001$). Suppression was achieved with LA 3.75 mg/28 days in all patients (70/70) who were at Tanner stage 2, in 87.6% of patients (106/121) at Tanner stage 3 and 76% of patients (19/25) at Tanner stage 4 at the time of diagnosis, while all patients (4/4) at Tanner stage 5 required 7.5 mg LA for the suppression of the HPG axis.

A comparison of the clinical and laboratory findings at the time of diagnosis of the patients for whom HPG axis suppression was achieved with 3.75 mg and 7.5 mg LA dosages revealed that those requiring 7.5 mg LA for suppression were found to have higher mean body weight, BMI, BMI-SDS values and elevated mean baseline LH, estradiol and peak stimulated LH levels at the time of diagnosis (Table 1). Among the patients with successful suppression at a dose of 3.75 mg LA, suppression was achieved with a mean dose of 0.11 ± 0.03 mg/kg, whereas in the patients for whom 3.75 mg dose was not adequate for suppression, the initially given dose of 0.08 ± 0.02 mg/kg (3.75 mg in total) was insufficient due to high body weight, and suppression was only achieved when these patients received dose of a 7.5 mg LA (0.16 ± 0.03 mg/kg).

ROC curves were used to determine the threshold levels for the factors which may affect the dose that achieved pubertal suppression. The best threshold values that differentiated the two doses (3.75mg/28 days vs 7.5mg/28 days LA) were 36.2 kg for body weight (AUC:0.934, $p:0.0001$, sensitivity:100%, specificity:66.7%), 20.7 kg/m² for BMI (AUC:0.964, $p:0.0001$, sensitivity:94%, specificity:74%), +1.64 for BMI-SDS (AUC:0.914, $p:0.0001$, sensitivity:100%, specificity:71.2%), 1.5 IU/L for basal LH (AUC:0.710, $p:0.0004$, sensitivity:68%, specificity:67%), 41 pg/ml for basal estradiol (AUC:0.898, $p:0.0001$, sensitivity:100%, specificity:68%) and 17.6 IU/L for peak stimulated LH (AUC:0.710, $p:0.0006$, sensitivity:68%, specificity:67%) in ROC analysis. Age did not differ between the two different dose populations (8.2 ± 1.0 vs 8.3 ± 0.5). Univariate analysis indicated BW, BMI and BMI-SDS above the defined thresholds as well as advanced stage of puberty were associated with higher dose of LA ($p < 0.001$, < 0.001 , < 0.001 , 0.02, respectively) (Table 2). However thresholds for basal LH, estradiol and stimulated LH peak did not differentiate between the two doses of LA since they were insignificant in the univariate analysis. Since BW and BMI-SDS were related factors, these factors were not used together in multiple regression analysis but instead used in separate regression models. Multiple logistic regression showed that thresholds for BMI-SDS and BW were significant to differentiate the two doses of LA ($p < 0.001$) (Table 3&4), whereas thresholds for basal LH, estradiol and stimulated LH peak did not differentiate the two dose groups, thus cannot be used to assess dose of LA required to suppress puberty.

Discussion

In this study we showed that leuprolide acetate treatment in doses of 3.75 mg/28days was effective in suppressing HPG axis in 88.6% of girls with iCPP, while suppression was achieved in the remaining 11.4% of cases through doses of 7.5 mg/28 days. Suppression of the HPG axis can be achieved in 85-96 % of the cases using a dose of 3.75 mg/28 days LA in studies from Europe and Brasil (7, 9, 21, 22). Studies carried out in the United States, report higher LA doses, i.e. 7.5 mg/monthly or more for HPG suppression (23, 24). In Japan Tanaka et al. compared doses of 10, 30 and 90 mcg/kg in 36 children with CPP (90 mcg/kg being roughly equal to 3.75 mg LA) and concluded that minimum suppressive dose of LA is 30 mcg/kg, which is one tenth of the US recommendations and much lower than the dose of 3.75 mg/28 days (25).

Recently, use of three-monthly LA depot preparations in pediatric patients appeared in the literature (26). A similar dose difference in the use of LA depot formulations seems to linger on between United States and Europe. In a French study of 40 cases with CPP, a three-monthly dose of 11.25 mg provided suppression of GnRH-stimulated gonadotropin levels (27). In a study in the United

States, Fuld et al. compared three doses of LA (LA 7.5 mg/month, 11.25 mg/3 months and 22.5 mg/3 months) in 54 patients with CPP, and showed that the dose of 22.5 mg/3 months provided a better suppression of LH levels in comparison to a dose of 11.25 mg/3 months. However, these last two doses did not differ in their effect on other parameters (i.e. growth velocity, progression of bone age or estradiol levels) (28). Mericq et al. compared the same three doses of LA on 14 children, and recommended the use of high-dose LA depot formulations in cases with a body weight of more than 30 kg, although LA depot formulation at a dose of 11.25 mg/3 months also provided sufficient (75%) pubertal suppression (29).

One major constraint in the published studies is that they were carried out in small populations of children. What's more, many studies analyzed mixed populations with respect to sex (involving both girls and boys) and etiology (both idiopathic and organic cases were included). The GnRHa dose required to suppress the HPG axis may differ between girls and boys, and also between CPP cases of organic etiology vs idiopathic ones. Also most studies comparing monthly vs three monthly preparations did not include LA in the dose of 3.75mg/28 days.

There is one study from USA which included monthly 3.75 mg LA and compared it with 7.5 mg/month and 11.25 mg/3 months LA. In that study Badaru et al. showed that peak depot LA stimulated LH and FSH levels using a dose of 3.75 mg/month and 11.25 mg/3 months were higher than those using a dose of 7.5 mg/month (26) (the mean depot LA-stimulated LH was 1.30 ± 0.74 , 1.73 ± 0.99 and 2.13 ± 1.41 , with doses of 7.5 mg/month, 3.75 mg/month, and 11.25 mg/3 months, respectively). However, the authors underlined that clinically significant elevation to merit dose escalation was observed only in a small number of patients. In addition serum estrogen levels did not differ between the three dose regimens.

In the current study we analyzed a large homogenous population of girls with iCPP to see if pubertal suppression can be achieved with lower monthly doses of LA. We also analyzed the suppressive dose of LA against factors that may impact on its effect. We hypothesized that such an analysis may help predict the dose of LA that can suppress puberty and avoid high doses of LA along with its adverse effects. The current study suggests that LA in the dose of 3.75 mg/28days effectively suppresses HPG axis in most of the girls with iCPP. A comparison of the two populations (pubertal suppression by LA 3.75 mg/28 days vs 7.5 mg/28 days) showed that there was significant difference between them in several clinical and laboratory parameters such as body weight, BMI, basal LH, estradiol, and peak stimulated LH in the initial GnRH test. As would be expected, higher GnRHa doses may be required for pubertal suppression in cases at advanced stages of puberty. Similarly, the patients who required dose escalation had higher baseline LH and estradiol levels as well as higher peak LH in the GnRH test. We showed that the most significant factors pointing to a need for LA at a dose of 7.5 mg/28 days were body weight ≥ 36.2 kg, and BMI-SDS ≥ 1.64 .

In general, the use of high dose of GnRHa may have two important consequences. First, oversuppression of puberty using a high dose of GnRHa may carry the risk of suppression of growth. Second, extensive pubertal suppression may affect BMD adversely, since long-term oversuppression of estrogen may decrease bone mineral accrual. In addition, high dose would increase treatment costs excessively. It is well-known that one major purpose of GnRHa treatment is to increase the final height potential. Thus it may seem contradictory to suggest that oversuppression of puberty may adversely affect growth. Studies investigating long-term effects of GnRHa treatment have shown the expected deceleration in bone age advancement as well as suppression of puberty increasing final height (30). However, these studies did not address the relation between height gain and the dose of GnRHa used to suppress puberty.

Mitamura et al studied 24 hour gonadotropin and sex steroid profile in 17 girls (5-11.5 years) and showed that diurnal rhythm of gonadotropins were present in all subjects including those aged 5-6 years (31). Also 1/3rd of their prepubertal subjects had elevated early morning estradiol. They suggested that preparation for the onset of female puberty may begin in 5-to 6-yr-old girls. Lampit et al compared GnRHa therapy with and without mini dose estrogen in a small number of patients. (32). They showed that during GnRH agonist therapy a mini-dose of estrogen effectively maintains normal prepubertal growth without acceleration of bone maturation for at least 24 months, whereas growth velocity may decrease in those receiving GnRHa alone.

Currently it is not clear whether over suppression of HPG axis would do more harm than good in terms of growth, since this issue is not specifically addressed. Moreover it is not known whether

such an oversuppression even if it decreases growth velocity, would also affect final height adversely. Unfortunately, long-term results of high dose LA (7.5 mg/28 ds or higher) are scarce, and no study compared long term height gain with low vs high dose of LA. Extensive suppression of growth may be unwanted. Thus studies are required to specifically address these issues.

Puberty is the critical period for bone development and accrual of peak bone mass (33). Approximately half of the peak bone mass is acquired during puberty (34). Postmenopausal decrease in bone mineral density (BMD), as well as reduction of BMD in premenopausal adults using GnRHa treatment is attributed to hypo-estrogenism. GnRHa therapy for CPP is also suggested to create a hypo-estrogenic condition which may have a negative impact on bone mass (34). There are contradictory reports to that effect in children. Some studies report a decrease in BMD in children using GnRHa therapy, whereas in others no difference was shown in BMD during treatment (35, 36). Most studies were carried out using 3.75mg/28 days of LA. Oversuppression of HPG axis with 7.5mg/28 days or higher doses may have a stronger negative impact on accrual of bone mineral. There is a need for long-term, randomized trials investigating the impact of high dose of LA on bone health in children with CPP.

Another disadvantage of unnecessary high-dose LA treatment is that it is costly. Healthcare costs have been increasing all over the world in the last decades, and there is an increasing pressure worldwide to reduce costs and improve efficiency, while maintaining quality. Thus expensive treatments without added benefit to health is an issue of consideration.

The present study has several advantages in terms of its sample size, choice of patient population. It also provides an analysis of factors that may affect the suppressive dose of LA in a large sample of 220 girls with iCPP, and provides a strategy based on body weight in the choice of the initial dose of LA for pubertal suppression. Another advantage is the use of gold standart GnRH test to assess pubertal suppression.

Study Limitations

Dose titration was not carried out in this study. LA was used 3.75 mg initially and 7.5 mg in those with inadequate suppression. This approach cannot provide minimum effective dose for successful suppression.

Conclusion

Monthly injections of LA (3.75 mg/28 days) is an effective treatment in terms of HPG axis suppression in majority of girls with iCPP. This treatment option is also more cost-effective than an initial high dose of 7.5 mg/28 days dose. Higher initial dose may be preferred in patients with a body weight ≥ 36 kg or BMI-SDS ≥ 1.6 for effective suppression of HPG axis and these patients require closer clinical follow-up. Further studies comparing long term impact of different doses of GnRHa on growth and bone health are required.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Table 1. Comparison of clinical and laboratory characteristics of the patients treated with LA 3.75 mg vs 7.5 mg

	3.75 mg LA (n:195)	7.5 mg LA (n:25)	p value
Age at diagnosis (years)	8.2±1.0	8.3±0.5	0.535
Bone age (BA) (years)	10.2±0.9	10.3±0.9	0.422
Body weight (kg)	32.1±6.1	44.9±7.1	<0.001
BMI (kg/m ²)	18.7±3.3	27.5±8.4	<0.001
BMI-SDS	1.1±1.2	2.4±1.2	<0.001
Height (cm)	135.2±9.2	136.2±10.0	0.172
Height-SDS	1.1±1.2	1.1±1.3	0.991
Height-SDS for BA	-0.6±1.0	-0.5±1.2	0.833
Basal FSH (IU/L)	4.5±2.1	5.3±2.5	0.121
Basal LH (IU/L)	1.2±0.7	1.9±1.2	<0.001
Basal Estradiol (pg/ml)	30.6±14.4	52.5±9.1	<0.001
Peak stimulated LH (IU/L)	11.7± 5.0	16.7±9.4	<0.001
Age at 6 months post-treatment (years)	8.7±1.0	8.8±0.5	0.546
Bone age at 6 months post-treatment (years)	10.5±1.2	10.6±1.2	0.624
Height-SDS at 6 months post-treatment	1.1±1.2	1.1±1.3	0.991
Basal LH at 6 months post-treatment (IU/L)	0.3±0.3	0.3±0.3	0.848
Basal Estradiol at 6 months post-treatment (pg/ml)	12.5±2.5	13.4±3.2	0.434
Age at 12 months post-treatment (years)	9.2±1.0	9.3±0.5	0.485
Bone age at 12 months post-treatment (years)	11.0±1.3	11.2±1.2	0.626
Height-SDS at 12 months post-treatment	1.0±1.2	1.0±1.2	0.866
Basal LH at 12 months post-treatment (IU/L)	0.2±0.2	0.2±0.2	0.824
Basal Estradiol at 12 months post-treatment (pg/ml)	10.3±1.6	10.4±1.8	0.386

Table 2. Factors affecting treatment dosage based on a univariate logistic regression analysis

Variables	Odds Ratio	95% CI		P-value
Body weight \geq 36.2 kg	1.619	1.330	1.914	<0.001
BMI \geq 20.7 kg/m ²	1.941	1.515	2.488	<0.001
BMI-SDS \geq 1.64	2.165	1.735	2.690	<0.001
Basal LH \geq 1.5 IU/L	1.084	0.898	1.309	0.401
Basal Estradiol \geq 41 pg/ml	1.004	0.995	1.014	0.330
Peak stimulated LH \geq 15.7 IU/L	1.240	0.742	1.726	0.421
Pubertal Stage (Advanced vs early)	2.516	0.877	7.215	0.020

Table 3. Factors affecting treatment dose based on multivariate logistic regression analysis (First model)

Variables	Odds Ratio	95% CI		P-value
BMI-SDS \geq 1.64	2.846	1.268	6.324	<0.001
Pubertal Stage (Advanced vs early)	2.247	0.382	26.263	0.489

Table 4. Factors affecting treatment dose based on multivariate logistic regression analysis (Second model)

Variables	Odds Ratio	95% CI		P-value
Body weight \geq 36.2 kg	2.134	1.646	3.116	<0.001
Pubertal Stage (Advanced vs early)	3.212	0.525	14.284	0.365