A Randomized Trial of 1- and 3-Month Depot Leuprolide Doses in the Treatment of Central Precocious Puberty

Kimberly Fuld, DO, Carolyn Chi, MD, and E. Kirk Neely, MD

Objective To compare 1-month and 3-month depot formulations of leuprolide acetate (DL), a gonadotropin-releasing hormone analog, in the treatment of central precocious puberty (CPP).

Study design Subjects with CPP naïve to therapy were randomized to 7.5 mg of 1-month DL, 11.25 mg of 3-month DL, or 22.5 mg of 3-month DL. Stimulated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and estradiol levels, growth velocity, and bone age progression were examined in a 2-year period.

Results Forty-nine female and 5 male subjects with CPP were randomized. Mean stimulated LH and FSH levels during treatment were higher in the low-dose 11.25-mg 3-month DL group, and more LH levels >4 IU/L were observed, in comparison with the other two dose groups. Mean LH and FSH levels in the 22.5-mg 3-month group were not different from the monthly DL. No differences in estradiol levels, growth velocity, or bone age progression were observed in dosing groups.

Conclusions All DL doses resulted in prompt and effective suppression of puberty, but higher LH and FSH levels were seen with the 11.25-mg 3-month DL dose. Multi-monthly DL is effective in treating CPP, but higher dosing may be required in some circumstances. *(J Pediatr 2011;159:982-7)*.

Central precocious puberty (CPP) is defined as early activation of the hypothalamic-pituitary-gonadal axis leading to the development of early sexual maturation in children. Gonadotropin-releasing hormone (GnRH) analogs are the mainstay of treatment for CPP.[1-4] These GnRH agonists act as potent inhibitors of gonadotropin secretion, leading to decreased sex steroid production and cessation of pubertal progression.

Depot preparations of leuprolide acetate (DL) are preferred to daily subcutaneous preparations because of improved compliance and efficacy. However, dosing variation exists among pediatric endocrinologists worldwide. In the United States, the recommended starting dose of monthly DL is 0.3 mg/kg within a 7.5 to 15.0 mg range given intramuscularly (IM) at 4-week intervals. In contrast, the minimum starting dose in Europe and Asia is consistently lower, because both Japanese and French investigators have reported successful long-term pubertal suppression in CPP with 3.75 mg every 4 weeks.[5,6]

Multi-monthly formulations of DL, commonly used in adults to treat prostate cancer and endometriosis,[7,8] have come into wider use for treatment of CPP to decrease the burden of injections and clinic visits. However, few comparison studies are available investigating the efficacy of monthly and various multi-monthly DL preparations, potentiating the risk of either inadequate suppression or overexposure in these children. Carel et al[9] reported good pubertal suppression with 3-month 11.25 mg of DL in a large population, but the gonadotropin and estradiol (E2) assays used were relatively insensitive. Badaru et al[10] investigated the efficacy of lower dose 1-month 3.75-mg and 3-month 11.25-mg DL compared with higher dose 1-month 7.5-mg DL in a sequential dose comparison. They found that stimulated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were slightly but significantly higher with both of the lower-dose regimens, but no differences were seen in sex steroid suppression or other clinical measures. A recent small study of 1-month and 3-month DL doses reported adequate and comparable hormonal suppression for 1 year.[11] In this study, we report the results of a larger randomized dose comparison trial of 2-year duration with 1-month and 3-month DL preparations.

Methods

Beginning in 2005, all patients in the Pediatric Endocrine Clinic at Lucile Packard Children's Hospital at Stanford who were commencing GnRH analog therapy for CPP were invited to participate in the study. CPP in girls was defined clinically as onset

CPP	Central precocious puberty
DL	Depot preparations of leuprolide acetate
E2	Estradiol
FSH	Follicle stimulating hormone
GnRH	Gonadotropin-releasing hormone
IM	Intramuscularly
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
LH	Luteinizing hormone
PAH	Predicted adult height

From the Drexel University College of Medicine, Philadelphia, PA (K.F.); Baylor College of Medicine, Houston, TX (C.C.); and Stanford University, Stanford, CA (E.N.)

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of breast development before 8.0 years of age. CPP in boys was defined as Tanner 2 genital stage and testicular volume >4 cc before 9.0 years of age. Minimal laboratory inclusion criterion was a random LH level >0.3 IU/L[12,13] or aqueous leuprolide-stimulated LH level >5 IU/L[14-16] performed with immunochemiluminometric assay (see below). Some pubertal patients exceeding the age criterion began GnRH analog therapy for augmentation of growth and were included in the study. Written informed consent was obtained from the parents of all participants before enrollment, and a written assent was obtained from children >7 years old. The protocol and consents were approved by the Stanford University Administrative Panel on Human Subjects in Medical Research.

Protocol

Participants were initially randomized to either monthly depot leuprolide acetate (Lupron Depot-Ped, Abbott, Abbott Park, Illinois) 7.5 mg IM every 4 weeks or the depot leuprolide acetate (Lupron Depot) 11.25-mg 3-month preparation IM every 12 weeks. Early in the study, a third arm using the 22.5-mg 3-month DL preparation was added to the randomization scheme (**Figure 1**; available at www.jpeds.com). At the 48-week visit, subjects on the 7.5-mg 1-month dose were converted to the 11.25-mg 3-month dose. In the final year of enrollment, randomization to the 7.5-mg 1-month DL arm was terminated, and all new subjects were randomized to the 11.25-mg 3-month dose or 22.5-mg 3-month dose. Patients with stimulated LH >6 IU/L at two separate visits or evidence of injection reaction were discontinued. Subjects with stimulated LH levels higher than the conventional cutoff threshold of 4 U/L but <6 IU/L continued in study.

Evaluation and Laboratory Testing

History and physical examination, including pubertal stage and 3 height measures, were obtained every 12 weeks for 96 weeks. Bone age radiographs were performed at baseline, 48 weeks, and 96 weeks and interpreted by the radiology division of the Packard Hospital at Stanford according to the standards of Greulich and Pyle, and predicted adult height (PAH) was calculated with the Bayley-Pinneau tables.[17] A venous blood sample was drawn 40 minutes after DL injection[18,19] or an aqueous leuprolide injection[14-16] at alternating visits, with stimulation tests obtained after the therapeutic DL injection at weeks 0, 24, 48, 72, and 96, and after aqueous leuprolide acetate (Sandoz, Princeton, New Jersey) at weeks 12, 36, 60, and 84. Basal hormone samples were not obtained. LH and FSH assays were performed with immunochemiluminometric assay at Esoterix (Calabasas Hills, California), with thresholds of sensitivity of 0.02 IU/L.[13] E2 assay was performed initially with radioimmunoassay (Esoterix), with a lower threshold of detection of 5 pg/mL. In the first year of the study, Esoterix introduced liquid chromatography/tandem mass spectrometry (LC-MS/MS), with a lower level of sensitivity of 1 pg/ml. Only LC-MS/MS E2 data were included in data analysis.

Statistics

Differences in dose groups in LH, FSH, and E2 levels, growth velocity, weight change, bone age advancement, and PAH were evaluated with *t* test. Correlations among LH, FSH, and E2 levels and between those measures and weight or weight-adjusted dose (mg/kg/month) were performed with regression analysis. Subjects with physical evidence of injection reaction (n = 2) were discontinued from the study and excluded from calculations. Patients with potential growth anomalies, such as recently treated profound hypothyroidism or Russell-Silver syndrome, were excluded from growth and bone age analysis. Boys were included for evaluation of LH and adverse events, but were excluded from calculations of FSH, growth rate, and bone age advancement.

Results

Characteristics of the 54 enrolled subjects are shown in **Table I**. Mean age at the start of DL therapy for all subjects was 8.1 ± 1.9 years, including 4 patients with diagnoses other than precocious puberty, who were older on average. Most subjects in all groups had a diagnosis of idiopathic CPP. There were no significant differences in starting age, height, weight, and bone age when comparing the 3 dose groups. The initial mean stimulated LH and E2 levels also did not differ in dose groups. However, the mean stimulated FSH level was lower in the 22.5-mg 3-month group when compared with the 7.5-mg 1-month and 11.25-mg 3-month dose groups.

Gonadotropin and Sex Steroid Suppression

Mean stimulated levels of LH, FSH, and E2 decreased significantly in all dose groups between baseline and all subsequent treatment visits. All levels were obtained 40 minutes after leuprolide injection, alternating by visit between stimulation with free leuprolide in the DL injection itself versus a separate aqueous leuprolide stimulation test before the DL injection. No differences were observed in the mean LH, FSH, and E2 levels obtained with the respective methods.

LH levels were higher in the 11.25-mg 3-month dose group when compared with the 7.5-mg 1-month dose group at all visits in the first year, as shown in **Figure 2**. Mean stimulated LH concentrations in the first year were 1.56 ± 0.94 IU/L, 2.52 ± 1.13 IU/L ($P < .001$ versus both other groups), and 1.63 ± 0.76 IU/L in the 7.5-mg 1-month, 11.25-mg 3-month, and 22.5-mg 3-month groups, respectively. No differences between the 22.5-mg 3-month and 7.5-mg 1-month dose groups were observed. The incidence of subjects with stimulated LH levels >4 IU/L during the first year of therapy was higher in the 11.25-mg 3-month group (7/21 subjects, of which 4/7 had elevated LH level at more than one visit) compared with the 7.5-mg 1-month group (1/18 subjects) or the 22.5-mg 3-month group (1/13 subjects). LH levels >4 IU/L were less common in the second year overall, occurring only in 3 subjects in the 11.25-mg 3-month group, two of whom had been

Table I. Subject characteristics at baseline (±SD)

	7.5-mg 1-month	11.25-mg 3-month	22.5-mg 3-month
Subjects			
Total 54	19	21	14
Male*	2	1	2
Mean age, years	8.3 ± 2.2	8.1 ± 1.4	7.8 ± 2.2
Mean bone age, years	10.3 ± 2.4	10.0 ± 1.9	10.1 ± 2.3
Mean height, cm	134.0 ± 13.7	131.6 ± 8.8	134.9 ± 6.0
Mean weight, kg	37.3 ± 12.3	30.0 ± 5.3	35.3 ± 7.2
Mean dose for weight, mg/kg/month	0.239 ± 0.100	0.129 ± 0.025	0.214 ± 0.045
Diagnosis			
Idiopathic CPP	15	17	9
Central nervous system tumor	2	0	2
Other†	2	4	3
Mean stimulated LH level, IU/L	21.8 ± 21.9	22.9 ± 20.1	16.9 ± 12.7
Mean stimulated FSH level, IU/L	12.6 ± 5.6	13.9 ± 7.4	8.1 ± 4.4‡
Mean E2 level, pg/mL	21 ± 16	16 ± 11	24 ± 32

*Male subjects are excluded in summary statistics except for LH.
†Includes seizure disorders, congenital infection, meningitis, holoprosencephaly, and primary hypothyroidism.
‡$P < .01$ comparing mean FSH 22.5 mg with 7.5 mg and 11.25 mg.

converted from monthly DL (one described below), and in all 3 cases limited to a single visit. Mean LH level in the 11.25-mg 3-month group decreased from year 1 to year 2 ($P = .03$), but remained higher than mean LH level in the 22.5-mg 3-month group in year two (2.11 ± 1.03 versus 1.63 ± 0.91 IU/L, $P = .03$).

Three subjects exhibited LH levels >6 IU/L during therapy, one from each dose group. A 2-year-old girl with hypothalamic hamartoma in the 22.5-mg 3-month group demonstrated persistent LH level elevation at 7 to 8 IU/L through the 36-week visit and was changed to the histrelin implant with improved suppression. A 6-year-old boy with hamartoma had a transient LH level rise on switching in year 2 from monthly to 11.25-mg 3-month dose, but his LH level was suppressed at the next visit. A girl receiving monthly DL showed a progressively rising LH level to 12 IU/L at the 24-week visit with increasing signs of injection reaction that resolved after conversion to daily leuprolide. Additionally, a sterile abscess developed in a boy receiving the 22.5-mg 3-month dose after the second injection, necessitating surgical debridement and discontinuation of therapy, but he did not have documented LH failure. In total, 3 subjects required alternate therapies, none from the 11.25-mg 3-month group.

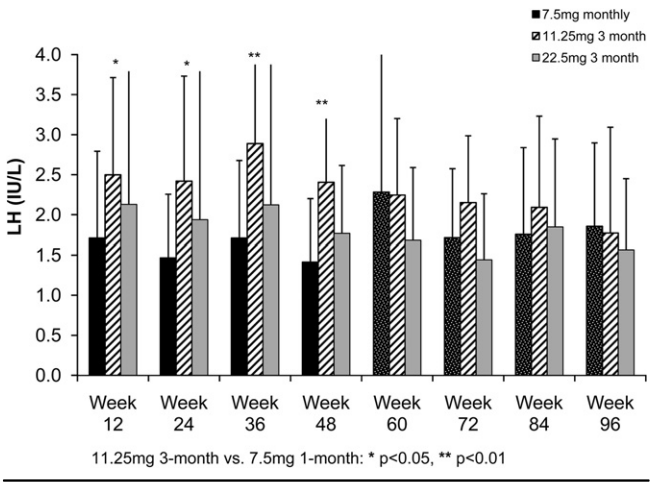

Figure 2. Concentrations of leuprolide-stimulated serum LH (mean ± SD) at 12-week visits in the 3 DL dose groups. Change in shading after week 48 in the 7.5-mg 1-month group indicates the switch to 11.25-mg 3-month dosing in year 2.

Mean FSH values trended higher in the 11.25-mg 3-month dose group at all visits in the first year compared with the other two groups (**Figure 3**). Mean FSH concentrations in the first year were 3.14 ± 2.05 IU/L, 3.72 ± 1.93 IU/L, and 2.82 ± 1.27 IU/L in the 7.5-mg 1-month, 11.25-mg 3-month, and 22.5-mg 3-month groups, respectively. Mean FSH level in the lower dose 3-month group was significantly higher compared with the 22.5-mg 3-month group ($P = .004$). No differences in FSH levels were observed between the monthly and 22.5-mg 3-month groups. FSH levels during therapy correlated weakly with LH levels ($r = 0.268$, $P < .001$).

In the second year, the 7.5-mg 1-month group was converted to 11.25-mg 3-month dosing. Subsequent to this transition, an unexpected and significant rise in mean FSH levels was observed in this group during year 2 compared with year 1 and in comparison with the 22.5-mg 3-month group. Mean FSH level rose from 3.1 ± 1.8 IU/L at the 48-week visit to 5.4 ± 1.5 IU/L at the 60-week visit ($P < .001$), the first visit after switching to the 11.25-mg 3-month injection. LH levels did not rise significantly after the transition from monthly DL to 11.25-mg 3-month.

Mean E2 levels were not different in dose groups (**Figure 4**; available at www.jpeds.com). Mean E2 levels throughout both years of study in all 3 groups were in the range of 1.2 to 2.4 pg/mL. Thirty-eight percent of levels were less than the detection limit of 1 pg/mL, and 97% were <5 pg/mL. The highest individual E2 level observed during the study was 10 pg/mL. None of the E2 levels >5 pg/mL was associated with LH >2.5 IU/L. E2 concentrations during

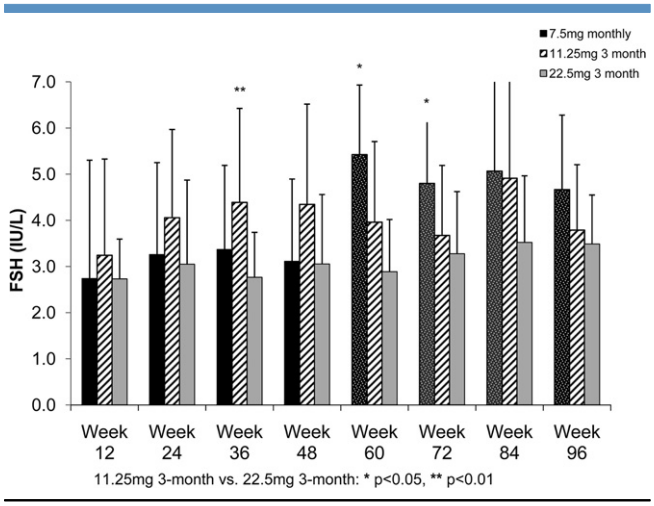

Figure 3. Concentrations of leuprolide-stimulated serum FSH (mean ± SD) at 12-week visits in the 3 DL dose groups. Change in shading after week 48 in the 7.5-mg 1-month group indicates the switch to 11.25-mg 3-month dosing in year 2.

treatment did not correlate with stimulated LH concentrations (r = 0.064), but E2 did correlate weakly with FSH (r = 0.165, P = .008).

Of the 5 boys treated in the study, none had idiopathic CPP (3 central nervous system tumors, 2 structural anomalies). Mean age at baseline was 9.1 ± 2.4 years. The mean baseline LH level of 18.3 IU/L was not different from that of female subjects, and suppression to an overall mean LH level of 2.1 ± 0.7 IU/L during the first year of therapy regardless of treatment group was also comparable. The baseline mean testosterone level of 118 ng/dL decreased to a first-year treatment mean of 7 ng/dL, with only one boy ranging greater than the 10 ng/dL pubertal threshold at two visits, to 19 and 20 ng/dL, respectively.

Change in Height, Weight, Bone Age, and Predicted Adult Height

Height velocity was similar in all groups and consistent with regression to a normal prepubertal rate during treatment (Table II). There was an insignificant trend toward a decreasing height velocity in all groups in the second year of treatment. Growth velocity in the boys was similar to that in the girls (5.4 cm/year first year). Bone age advancement was not significantly different in the dose groups at any visit (Table II), and likewise, the change in PAH did not differ in groups. Mean PAH in the 11.25- and 22.5-mg 3-month dose groups at baseline were 158.0 and 158.2 cm, respectively, and at 2 years, they were 160.8 and 158.1 cm, respectively. Mean weight gains in 2 years were 9.0 ± 3.8 kg, 7.8 ± 2.9 kg, and 13 ± 6.0 kg in the 7.5-mg 1-month, 11.25-mg 3-month, and 22.5-mg 3-month groups, respectively. Weight gain in the higher dose 3-month group (which trended heavier at baseline) was significantly greater compared with the lower dose 3-month group, but not compared with the 1-month group.

Effect of Weight on Treatment Outcome

Weight correlated positively with LH and FSH levels, but not E2 levels, with linear regression (LH r = 0.229, P = .003; FSH r = 0.219, P = .005; n = 162) for aggregate first-year treatment visits but not at any single visit. For further analysis, DL doses were adjusted for weight and duration by dividing the total dose by weight and by a factor of 3 for the 3-month preparations. The initial mean adjusted doses (mg/kg/month) for each study group are shown in Table I, with the average monthly dose delivered in the 11.25-mg 3-month group roughly half that seen in the other two groups, as expected. Linear regression of adjusted dose versus LH, FSH, or E2 for aggregate first-year visits revealed a significant inverse relationship between dose and LH (r = 0.275, P < .001) or FSH (r = 0.367, P < .001) (Figure 5; available at www.jpeds.com), but not E2. Correlation of dose with LH was significant at the 36- and 48-week visits and with FSH at the 24-, 36-, and 48-week visits. Adjusted dose did not correlate with LH within the dose groups themselves and specifically did not predict the occurrence of LH >4 IU/L within the 11.25-mg 3-month group. The initial dose in subjects receiving 11.25-mg 3-month DL with subsequent first year failure (LH >4, 0.138 ± 0.032 mg/kg/m; range, 0.108-0.194; n = 7) was not different from non-failures (0.124 ± 0.019; range, 0.91-0.158; n = 12). There were significant correlations between weight or adjusted dose and FSH within all 3 dose groups, with higher weight and lower dose associated with higher FSH levels.

Discussion

GnRH analogs are standard for treatment of CPP, and their efficacy and safety are well established.[1-4] We demonstrate in a direct randomized trial that 3-month DL has similar efficacy and safety compared with the monthly form. With either of the 3-month DL preparations, stimulated LH and serum E2 concentrations declined approximately 10-fold

Table II. Change in height, bone age, and weight in girls in years 1 and 2 by dosing group

	Height velocity (cm)		Δ Bone age (years)		Δ Weight (kg)	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
7.5-mg 1-month*	6.1 ± 1.7	5.3 ± 1.6	1.3 ± 0.9	0.9 ± 0.8	5.4 ± 3.7	4.1 ± 3.0
11.25-mg 3-month	6.0 ± 1.6	5.1 ± 1.9	1.0 ± 1.1	0.3 ± 0.9	5.1 ± 2.6	3.1 ± 0.9
22.5-mg 3-month	5.4 ± 1.8	4.7 ± 0.8	1.3 ± 1.1	0.9 ± 0.5	7.6 ± 2.2	6.5 ± 2.6

*Converted to 11.25-mg 3-month in year 2.

from baseline to the first follow-up visit and were sustained in that range for 2 years. Bone age advancement and growth velocity were comparably suppressed for 2 years by the monthly and multi-monthly preparations.

Suppression of stimulated LH is generally considered the single best short-term measure of treatment adequacy. We confirmed that aqueous leuprolide and depot leuprolide LH stimulation tests deliver interchangeable results; aqueous leuprolide stimulation is therefore unnecessary during routine DL therapy. We found no differences in LH suppression between the 7.5-mg 1-month and 22.5-mg 3-month doses. Because of the obvious convenience of multi-monthly dosing, this argues for routine clinical use of multi-monthly rather than monthly DL, although the latter remains the only US Food and Drug Administration-approved DL preparation for CPP at this time. However, we tested a fixed 7.5-mg monthly dose rather than weight-based dosing, and all 3 of our study groups received lower average DL doses than recommended by the manufacturer for monthly use in the United States. It remains a theoretic possibility that maximal monthly dosing might deliver LH suppression and clinical outcomes superior to multi-monthly dosing, with its inherently lower total dose delivered.

We confirmed that the 11.25-mg 3-month dose results in marginally inferior LH and FSH suppression compared with monthly DL. Additionally, FSH levels in particular rose in subjects who were switched from monthly DL to the lower dose 3-month DL in the second year. LH and FSH levels in the 22.5-mg 3-month group were consistently more suppressed compared with those in the 11.25-mg 3-month group, although our study was insufficiently powered to confirm the difference at each study visit. These results are generally consistent with our earlier sequential dose comparison study,[10] the Mericq pilot study,[11] and the multicenter short-term trial of 11.25-mg and 30-mg doses reported in abstract form.[20] The earlier large study of 11.25-mg 3-month by Carel et al[9] showed adequate biochemical and clinical outcomes, but did not use a monthly dose for comparison. Of clinical interest, our study was of longer duration than the other studies cited. As a result, we were able to observe that LH levels declined in the second year of 11.25-mg 3-month DL, and fewer LH levels >4 were evident.

We are unable to predict which patients might have higher stimulated LH levels on the 11.25-mg 3-month dose. Because we used fixed DL doses in all groups, weight is a reasonable candidate for association with LH or FSH suppression during therapy. DL dose in mg/kg/month was inversely correlated with LH and FSH levels during therapy in all groups combined, which restates the finding that mean LH and FSH are higher in the lower dose 3-month group. However, we could not find a relationship between weight and LH level within the 11.25-mg 3-month dose group itself. For unknown reasons, one-third of this group exhibited a LH level >4 IU/L at some point during therapy. Patients in our study with stimulated LH level of 4 to 6 IU/L were allowed to continue in the study, and almost all had a decline in LH with time. Anecdotally, pediatric endocrinologists have been concerned that boys and the youngest girls, particularly those with hypothalamic hamartomas, might be more likely to exhibit higher LH levels during therapy. In our small sample of boys, we found that stimulated LH during treatment was comparable with levels observed in girls. In our study only two of 54 children had a persistent elevation in LH level >6 IU/L, one associated with reaction to the standard monthly injection and the other a young girl with a hamartoma. It may be advisable to use the histrelin implant[20] in young patients with hamartomas.

What remains in question is whether the lesser degree of LH suppression associated with the 11.25-mg 3-month dose, transient or not, is clinically meaningful. Despite conventional wisdom, stimulated LH may not be the best measure of quiescence of the hypothalamic-pituitary-gonadal axis in the ranges achieved during therapy. We found that E2 correlated slightly better with stimulated FSH than with stimulated LH. In contrast to the LH differences detected, we found no group differences in E2 level, growth velocity, bone age advancement, or change in PAH in either year of treatment. None of the dose comparison studies to date have uncovered any differences in DL doses other than stimulated LH and FSH. A caveat is that pre-pubertal E2 levels are presumably not being measured with complete accuracy despite the use of ultrasensitive assays like LC-MS/MS.

The two CPP treatment options currently approved in the United States are monthly DL and the annual histrelin implant. Results of this study comparing monthly DL with multi-monthly alternatives suggest that continued use of the less convenient monthly dosing is not justified. Although a slight elevation in mean LH is observed with the lower 3-month DL dose, true treatment failures are no more common with either of the multi-monthly DL doses compared with the monthly. For routine clinical dosing of the multi-monthly DL, two acceptable approaches present themselves: beginning all subjects on 22.5-mg 3-month DL, which more closely approximates the total dose delivered by monthly therapy, or starting on the 11.25-mg dose, which is sufficient in most cases, then increasing the dose in the event that persistent hormonal or clinical criteria warrant. ■

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References

1. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Antoniazzi F, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123:e752-62.
2. Carel JC, Leger J. Clinical practice. Precocious puberty. N Engl J Med 2008;358:2366-77.
3. Neely EK, Lee PA, Bloch CA, Larsen L, Yang D, Mattia-Goldberg C, Chwalisz K. Leuprolide acetate 1-month depot for central precocious puberty: hormonal suppression and recovery. Intl J Pediatr Endocrinol 2010;398639.
4. Lee PA, Neely EK, Fuqua J, Larsen L, Yang D, Mattia-Goldberg C, Chwalisz K. Efficacy of leuprolide acetate 1-month depot for central precocious puberty (CPP): growth outcomes during a prospective, longitudinal study. Intl J Pediatr Endocrinol 2011;157878.

5. Tanaka T, Niimi H, Matsuo N, Fujieda K, Tachibana K, Ohyama K, et al. Results of long-term follow-up after treatment of central precocious puberty with leuprorelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function. The TAP-144-SR Japanese Study Group on Central Precocious Puberty. J Clin Endocrinol Metab 2005; 90:1371-6.
6. Carel JC, Lahlou N, Guazzarotti L, Joubert-Collin M, Roger M, Colle M, et al. Treatment of central precocious puberty with depot leuprorelin. French Leuprorelin Trial Group. Eur J Endocrinol 1995; 132:699-704.
7. Olive DL. Optimizing gonadotropin-releasing hormone agonist therapy in women with endometriosis. Treat Endocrinol 2004;3:83-9.
8. Persad R. Leuprorelin acetate in prostate cancer: a European update. Int J Clin Pract 2002;56:389-96.
9. Carel JC, Lahlou N, Jaramillo O, Montauban V, Teinturier C, Colle M, et al. Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11.25 mg). J Clin Endocrinol Metab 2002;87:4111-6.
10. Badaru A, Wilson DM, Bachrach LK, Fechner P, Gandrud LM, Durham E, et al. Sequential comparisons of one-month and three-month depot leuprolide regimens in central precocious puberty. J Clin Endocrinol Metab 2006;91:1862-7.
11. Mericq V, Lammoglia JJ, Unanue N, Villaroel C, Hernandez MI, Avila A, et al. Comparison of three doses of leuprolide acetate in the treatment of central precocious puberty: preliminary results. Clin Endocrinol 2009; 71:686-90.
12. Neely EK, Wilson DM, Lee PA, Stene M, Hintz RL. Spontaneous serum gonadotropin concentrations in the evaluation of precocious puberty. J Pediatr 1995;127:47-52.
13. Neely EK, Hintz RL, Wilson DM, Lee PA, Gautier T, Argente J, et al. Normal ranges for immunochemiluminometric gonadotropin assays. J Pediatr 1995;127:40-6.
14. Garibaldi LR, Aceto T, Jr., Weber C, Pang S. The relationship between luteinizing hormone and estradiol secretion in female precocious puberty: evaluation by sensitive gonadotropin assays and the leuprolide stimulation test. J Clin Endocrinol Metab 1993; 76:851-6.
15. Ibanez L, Potau N, Zampolli M, Virdis R, Gussinye M, Carrascosa A, et al. Use of leuprolide acetate response patterns in the early diagnosis of pubertal disorders: comparison with the gonadotropin-releasing hormone test. J Clin Endocrinol Metab 1994;78:30-5.
16. Bordini B, Littlejohn E, Rosenfield RL. Blunted sleep-related luteinizing hormone rise in healthy premenarcheal pubertal girls with elevated body mass index. J Clin Endocrinol Metab 2009;94:1168-75.
17. Bayley N, Pinneau MA. Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards. J Pediatr 1952;40:423-44.
18. Bhatia S, Neely EK, Wilson DM. Serum luteinizing hormone rises within minutes after depot leuprolide injection: implications for monitoring therapy. Pediatrics 2002;109:E30.
19. Brito VN, Latronico AC, Arnhold IJ, Mendonca BB. A single luteinizing hormone determination 2 hours after depot leuprolide is useful for therapy monitoring of gonadotropin-dependent precocious puberty in girls. J Clin Endocrinol Metab 2004;89:4338-42.
20. Eugster EA, Clarke W, Kletter GB, Lee PA, Neely EK, Reiter EO, et al. Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: a multicenter trial. J Clin Endocrinol Metab 2007; 92:1697-704.

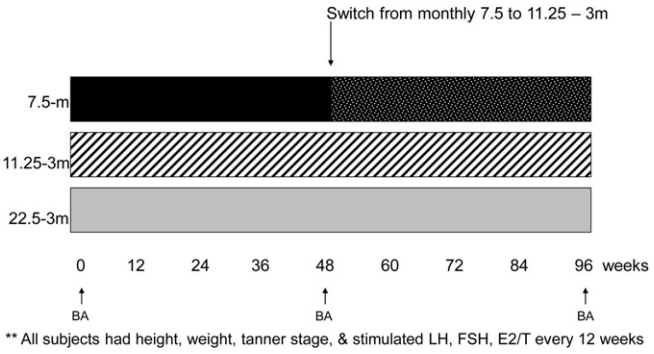

Figure 1. Study design showing the 3 dose groups in the 2-year study. *Arrow* and *change in shading pattern* depict the switch from 7.5-mg 1-month DL to 11.25-mg 3-month DL at 48 weeks.

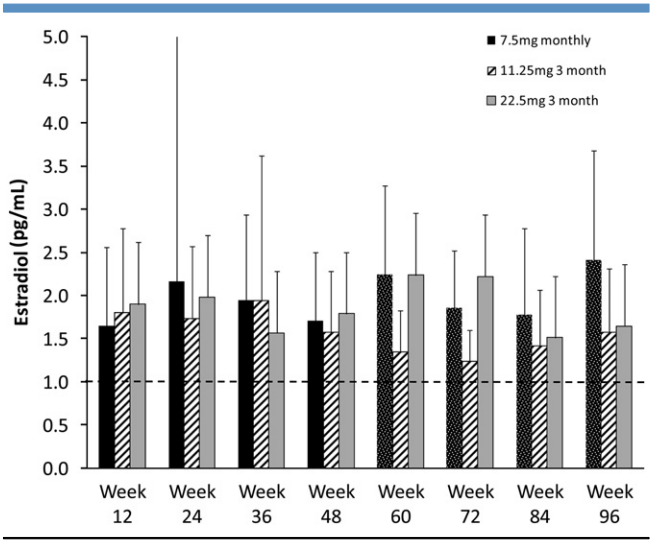

Figure 4. Concentrations of serum E2 (mean ± SD) at 12-week visits in the 3 DL dose groups. Change in shading after week 48 in the 7.5-mg 1-month group indicates the switch to 11.25-mg 3-month dosing in year 2. The dotted line designates the level of assay detection.

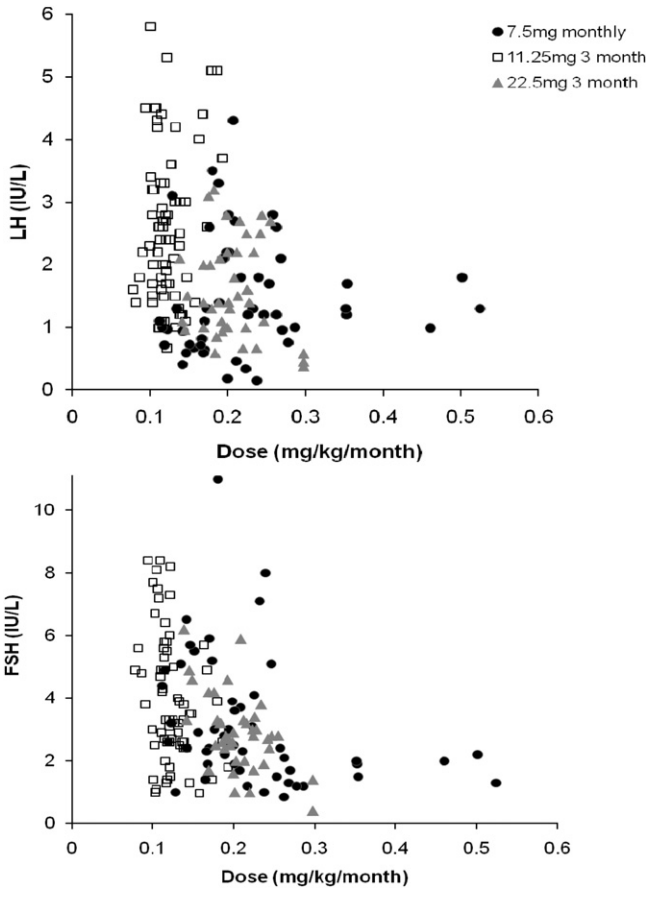

Figure 5. Upper panel, Correlation of stimulated LH and **Lower panel,** FSH with weight-adjusted depot leuprolide dose in mg/kg/month (3-month doses divided by 3) for treatment visits in female subjects during the first year (excluding treatment withdrawals).