Precocious puberty is usually defined as the appearance of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys.1

Gonadotropin-dependent precocious puberty, also known as central precocious puberty (CPP), is caused by the premature activation of gonadotropin releasing hormone (GnRH) pulse generator in the hypothalamus.2 It may be caused by intracranial organic lesions such as hamartoma, hydrocephalus and infection, or occur without obvious lesion. Patients with CPP usually have acceleration of the tempo of puberty and bone age maturation resulting in early fusion of epiphyseal growth plates and short adult height.3

Synthetic GnRH analogues (GnRHa) have been introduced as suppressive therapy for CPP since 1981.4 Continuous administration of GnRH will downregulate the GnRH receptors of the pituitary

The Effects of Gonadotropin Releasing Hormone Analogue Therapy on Girls with Gonadotropin-dependent Precocious Puberty

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Background/Purpose: It has been reported that gonadotropin releasing hormone analogue (GnRHa) therapy can improve the adult height of patients with gonadotropin-dependent precocious puberty. The purpose of this study was to evaluate the effect of GnRHa on the adult height of girls with gonadotropin-dependent precocious puberty and the adverse effects of such therapy.

Methods: Between 1989 and 2006, 11 girls with gonadotropin-dependent precocious puberty who had been treated with GnRHa and reached their adult height were enrolled in the present study. Follow-up studies of bone age, pelvic sonography and GnRH test were done regularly during the period of treatment. All patients had bone mineral density examined at least 2 years after completion of GnRHa therapy.

Results: GnRHa therapy was initiated at the age of 8.0 ± 1.5 years. The predicted adult height immediately before GnRHa therapy was 146.7 ± 4.8 cm (−2.3 ± 0.9 standard deviation [SD]). The duration of GnRHa therapy was 4.7 ± 1.8 years. The adult height of the patients was 156.3 ± 4.3 cm (−0.6 ± 0.8 SD), which is similar to their target height of 157.0 ± 4.5 cm (−0.5 ± 0.8 SD). The uterine sizes and gonadotropin responses to GnRH stimulation were well suppressed during treatment. Menstruation resumed 9.2 ± 5.9 months after the discontinuation of treatment in these patients. Forty-five percent of patients had lumbar bone mineral density less than 1 SD below that of normal young Taiwanese adults in the Taipei region.

Conclusion: GnRHa therapy can improve the adult height of patients with gonadotropin-dependent precocious puberty. However, 45% of patients had decreased bone accretion during therapy. [J Formos Med Assoc 2007;106(10):826–831]

Key Words: bone mineral density, GnRH analogue, precocious puberty

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gland and desensitize the pituitary response to GnRH, resulting in suppression of the secretion of downstream gonadotropins and sex hormones. There is some evidence that suppression of the abnormal progression of puberty in patients with CPP can prolong the period of growth in these children and improve their adult height.

There has been concern about the side effects of long-term GnRHa therapy in children. The recovery of the hypothalamus–pituitary–gonad axis and resumption of menstruation has been demonstrated. However, the effect on bone mineral density (BMD) is still inconclusive. Our study aimed to evaluate the efficacy of long-term GnRHa therapy and its possible adverse effects in Taiwanese girls with CPP.

Materials and Methods

Subjects
Between 1989 and 2006 at the pediatric endocrine clinic of National Taiwan University Hospital, there were 13 girls with CPP who had been treated with GnRHa and who reached their adult height. Two of them who had been treated with GnRHa and growth hormone because of the coexistence of growth hormone deficiency were excluded. Thus, 11 girls were enrolled for evaluation in the present study.

The etiologies of the 11 patients were as follows: three had hypothalamic hamartoma, one had post-traumatic hydrocephalus, and seven were classified as idiopathic. There was no statistically significant difference in the auxological data before treatment between these two groups except that the patients with central nervous system lesion had their onset of puberty at a younger age than those with idiopathic CPP (3.9 ± 1.7 years vs. 6.0 ± 2.4 years). Therefore, their data were grouped together in the discussion.

The 11 girls started GnRHa therapy at the age of 8.0 ± 1.5 years. All of the patients had demonstrated that their gonadotropin levels were responsive to GnRH stimulation before treatment, which was considered the criterion for the confirmation of their gonadotropin dependence. Their bone age at the start of treatment was 11.5 ± 1.3 years, which was advanced more than 2 standard deviations (SDs) above their chronological age.

Protocol
Before 1992, two patients had subcutaneous leuprolide acetate 40 µg/kg/day once daily as initial treatment, and depot preparation of subcutaneous triptorelin or leuporelin 3.75 mg once a month was prescribed after 1992 when the depot form of GnRHa became available in Taiwan. Three factors including (1) bone age > 14 years, (2) growth velocity < 2 cm/year or (3) the family’s satisfaction with the patient’s height were considered when deciding on the appropriate time to stop GnRHa therapy.

Patients’ height (measured with a stadiometer), weight and signs of puberty were evaluated once every 3 months. They underwent bone age study and pelvic sonography once every 6 months. Bone age was assessed according to Greulich and Pyle’s criteria. Predicted adult height (PAH) was calculated according to the method of Bayley and Pinneau. GnRH test was done at 3 months, 1 year and then once every 6 months after GnRHa therapy. The uterine volumes were measured by the same technician. Uterine size, including its length, and largest anteroposterior and transverse diameters, was measured using ultrasonography, and uterine volume was estimated using the formula for a prolate ellipsoid. GnRH stimulation test was performed with intravenous GnRH 0.1 mg, and serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were measured at baseline, 30, 60, 90 and 120 minutes after GnRH stimulation. Adult height was measured when bone age exceeded 16 years and the growth rate was less than 0.5 cm per year. The adult height of these patients was measured at the age of 19.8 ± 2.0 years. We performed dual energy X-ray absorptiometry (DEXA) (Norland XR26; Norland Corp., Fort Atkinson, WI, USA) to determine vertebral BMD at L2 to L4 in these patients at least 2 years after completion of GnRHa therapy.
The data were compared with those of normal young Taiwanese adults in the Taipei region.

**Statistical analysis**

All auxological data are expressed as mean ± SD except the data in the figures. The grouping data were analyzed statistically using the Mann-Whitney U test. The paired data were compared by the Wilcoxon signed-rank test. A p value of less than 0.05 was considered statistically significant.

**Results**

Before treatment, serum FSH levels rose from 6.0 ± 2.9 mIU/mL to 15.3 ± 0.8 mIU/mL, and serum LH levels rose from 4.1 ± 3.4 mIU/mL to 29.7 ± 23.5 mIU/mL after GnRH stimulation.

After GnRHa therapy for 3 months, the peak FSH and LH levels after GnRH stimulation were 2.0 ± 1.2 and 1.3 ± 1.5 mIU/mL, respectively. As shown in Figure 1, the hypothalamus–pituitary–ovary axis was well suppressed during the period of GnRHa treatment. Pubertal response to GnRH test was observed within 6 months after the discontinuation of GnRHa treatment, and menstruation resumed 9.2 ± 5.9 months (range, 3 months to 2 years) after the discontinuation of therapy.

Five patients had vaginal bleeding during the first month after therapy and eight patients had their breast regress to Tanner stage I after therapy. As shown in Figure 2, the uterine volume of the patients decreased from 9.7 ± 4.0 cm³ to 4.3 ± 2.6 cm³ after GnRHa therapy for 6 months (p < 0.01). Their uterine volume remained stationary during the period of therapy and it increased to

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**Figure 1.** Peak follicle-stimulating hormone (FSH) and luteinizing hormone (LH) responses to GnRH stimulation in patients with gonadotropin-dependent precocious puberty during the course of GnRHa therapy. *p < 0.05 compared to the value at the start of therapy; ‡p < 0.05 compared to the value at the end of therapy. End = time of discontinuation of GnRHa therapy; End + 0.5 = 6 months after the discontinuation of GnRHa therapy. Data are expressed as mean ± SEM.

**Figure 2.** Evolution of uterine size in patients with gonadotropin-dependent precocious puberty during the course of GnRHa therapy. *p < 0.05 compared to the value at the start of therapy; ‡p < 0.05 compared to the value at the end of therapy. End = time of discontinuation of GnRHa therapy; End + 0.5 = 6 months after the discontinuation of GnRHa therapy. Data are expressed as mean ± SEM.
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22.7 ± 7.4 cm³ 6 months after the discontinuation of GnRHa therapy.

The target height of the patients in this study was 157.0 ± 4.5 cm (−0.5 ± 0.8 SD). They started GnRHa therapy at the age of 8.0 ± 1.5 years. As shown in Figure 3, the growth velocity was 7.3 ± 1.5 cm/year immediately before therapy, and decreased to 6.1 ± 1.5 cm/year at the first year, 3.9 ± 1.2 cm/year at the second year, and 3.2 ± 1.3 cm/year at the third year. As shown in Figure 4A, the progression of bone age was significantly decreased from 2.4 ± 1.4 years per year before therapy to 0.5 ± 0.7 years per year at the first year of therapy. Patients stopped GnRHa therapy at the age of 12.7 ± 0.9 years, with a bone age of 13.6 ± 0.6 years. At that time, their height was 149.0 ± 5.0 cm. Bone age increased 1.1 ± 0.4 years at the first year after the discontinuation of GnRHa therapy. During the course of 4.7 ± 1.8 years of GnRHa therapy (range, 3.0–8.0 years), their bone age increased 2.0 ± 1.6 years and their height gain was 19.0 ± 10.0 cm during the same period. Therefore, their adult height of 156.3 ± 4.3 cm (−0.6 ± 0.8 SD) was significantly higher than their PAH of 146.7 ± 4.8 cm (−2.3 ± 0.9 SD) at the start of therapy (p < 0.01), as shown in Figure 4B.

Except for local discomfort at injection sites, there were no other serious adverse effects noted during the course of treatment. BMD was determined when the patients were 20.0 ± 1.9 years old, which was 7.3 ± 2.5 years after the discontinuation of GnRHa therapy. The BMD of their lumber spine was 0.99 ± 0.13 g/cm³, which was −0.9 ± 1.0 SD (range, −2.4 to 0.8 SD) in comparison with the...
data of normal young Taiwanese adults in the
Taipei region. Five of the 11 patients (45%) had
their BMD below −1 SD, which was defined as
osteopenia. No correlation between BMD and
duration of treatment was found.

Discussion

Our study showed that the activated hypothala-
mus–pituitary–ovary axis of patients with CPP
was suppressed after 3 months of GnRHa therapy,
and it remained well suppressed throughout the
course of GnRHa therapy. In addition, the breast
decreased in size and remained in prepubertal
stage in most of the patients. Withdrawal bleeding
was also observed during the first month after
the start of GnRHa therapy in patients who had
well-developed uterus. The uterine size of treated
patients regressed rapidly within 6 months after
therapy and remained stationary throughout the
course of GnRHa therapy. All of these data reflect
the fact that the hypothalamus–pituitary–ovary
axis was effectively suppressed by GnRHa therapy.
This study also demonstrated that the inappro-
priate progression of bone age maturation was
slowed down by GnRHa therapy through a dep-
rivation of estrogen effect by the suppression of the
hypothalamus–pituitary–ovary axis in these pa-
tients. It was reported that the continuous growth
of patients under GnRHa therapy can improve
their adult height.16 In this study, the bone age of
the patients matured only 2 years during a course
of 4.7 years of treatment, while they grew 19.0 cm
during the same period of time. Thus, they had a
mean adult height of 156.3 cm (−0.6 SD), which
was close to their target height of 157.0 cm
(−0.5 SD) and significantly taller than their PAH
of 146.7 cm (−2.3 SD) at the start of GnRHa ther-
apy. These results are consistent with previously
reported data.11,12,16,17

The reversibility of suppression of the hypo-
thalamus–pituitary–ovary axis was also well
demonstrated in our patients. Their serum go-

nadotropin levels showed a pubertal response to
GnRH stimulation and their uterine size enlarged
within 6 months after the discontinuation of
GnRHa therapy. All experienced resumption of
menstrual flow within 2 years after the discon-
tinuation of GnRHa therapy. Such findings are
consistent with a previous report.9

The introduction of long-acting depot prepara-
rations of GnRHa has improved patient compli-
ance due to the advantage of a reduced frequency
of injection, which is one of the important fac-
tors that makes long-term compliance to sup-
pressive therapy possible.5,18,19 Except for local
pain at the injection sites, no other serious ad-
verse effects were detected in our patients during
the period of GnRHa therapy.

Bone mineral accretion is a complex process
and estrogen may play an important role in it.20–22
GnRHa therapy suppresses the hypothalamus–
pituitary–ovary axis, which theoretically may
decrease the accretion of bone mass, resulting in
osteopenia or osteoporosis. Forty-five percent
of the patients in this study had osteopenia in
contrast to previous reports where no significant
change in BMD was observed after GnRHa ther-
apy.11,23 On the other hand, Heger et al reported
that the lumbar spine BMD of CPP patients treated
with GnRHa was not significantly different from
that of control subjects, but they noticed that 15%
of their patients had osteopenia.12 Yanovski et al
also reported that 82% of their patients treated
with GnRHa had BMD more than 1 SD below the
population.24 Further studies are indicated to
clarify such a discrepancy. Studies on the preven-
tion of low BMD in CPP patients treated with
GnRHa have rarely been reported. Antoniazzi
et al found that the BMD in CPP patients treated
with GnRHa and calcium supplementation was
better preserved than the BMD of CPP patients not
given calcium supplementation.23 Further studies
are necessary to confirm this.

In conclusion, GnRHa therapy can effectively
suppress the prematurely activated hypothalamus–
pituitary–ovary axis and improve the adult height
of patients with gonadotropin-dependent preco-
cious puberty. However, reduced BMD is a possible
major side effect that should be seriously consid-
ered during long-term GnRHa therapy.
References


