

Clinical application of gonadotropin-releasing hormone analogs in children and adolescents

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= Abstract =

Although the increasing incidence of central precocious puberty (CPP) in Korea has recently raised public concerns about health and growth problems, there are many areas of uncertainty regarding the pathogenesis, diagnosis, and management of CPP. In this paper, we review the definition of precocity, the assessment of CPP, and the hormonal abnormalities that support the diagnosis. In addition, we review the practical guidelines regarding the clinical use of gonadotropin-releasing hormone analogs in children with CPP. Indications for treatment, determination of dosage, monitoring during treatment, and discontinuation of therapy are discussed. (*Korean J Pediatr* 2010;53:294-299)

Key Words: Central precocious puberty, Gonadotropin-releasing hormone analogs, Child, Adolescent

Introduction

Puberty is a transitional period characterized by rapid physiological changes, including growth spurts and maturation of the gonads and the brain. It entails progression from the first appearance of secondary sexual characteristics to full sexual maturation and fertility. While it is known that the onset of puberty is initiated by awakening of complex neuroendocrine machinery and an increase in pulsatile secretion of gonadotropin-releasing hormone (GnRH) in the hypothalamic-pituitary-gonadal (HPG) axis, the primary mechanisms are incompletely understood. The time of onset of puberty and its course are influenced by genetic factors and are modified by environmental factors, including socioeconomic factors, nutrition, general health, geography, altitude, intrauterine conditions, stress, climate conditions, and the light-dark cycle¹⁾. Puberty is considered precocious when the onset of puberty begins before the age of 8 years in girls and before the age of 9 years in boys²⁾. Precocious puberty is divided into two classes: central precocious puberty (CPP) and pseudoprecocious puberty. CPP is caused by premature reactivation of the HPG axis,

while pseudoprecocious puberty is unrelated to activation of the HPG axis. In our series of 948 patients referred for evaluation of signs of precocious puberty, the final diagnoses were as follows: early puberty (39%), premature thelarche (31%), CPP (27%), and pseudoprecocious puberty (1%)³⁾. About 95% of precocious puberty is in females and 90% of CPP in girls is idiopathic³⁾. Children with precocious puberty may experience problems in growth and psychosocial development. GnRH analogs (GnRHAs) are standard of care for the treatment of CPP to improve the final outcome. According to recent reports, an increasing incidence of advanced pubertal timing is being observed worldwide. This secular trend of advance is also apparent in Korean children and adolescents. According to the data from the Health Insurance Review and Assessment Service in Korea, the number of patients treated with GnRHAs has surprisingly increased from 226 patients in 2004 to 1,707 patients in 2008⁴⁾. The increasing incidence of precocious puberty has raised public concerns over health and growth problems. This review summarizes the optimal use of GnRHAs in children with CPP.

Diagnostic evaluation of CPP

1. Clinical criteria

Precocious puberty can be diagnosed when breast or pubic hair development begins before the age of 8 years

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or menstruation begins before the age of 9.5 years in girls and when testicular enlargement begins before the age of 9 years in boys. Although CPP usually presents with accelerated growth velocity and bone maturation, it does not present as a homogeneous clinical picture. CPP may be more appropriately described as a continuum of clinical presentation and rate of progression, ranging from a normal variant or transient form to slowly progressive or rapidly progressive forms (Fig. 1)⁵⁾. Premature thelarche can progress to progressive CPP. In addition, some forms of progressive CPP may present an unsustained or undulating course during progression^{6, 7)}. Patients with premature thelarche or the transient form of CPP and certain patients with slowly progressive CPP and advanced bone age may reach normal adult height without administration of GnRHAs. The recognition of progressive pubertal development is the most important clinical criterion for GnRHAs therapy for avoidance of unnecessary treatment. It is recommended that documentation of progressive pubertal development and accelerated growth should be made over a 3- to 6-month period prior to initiating GnRHAs therapy⁸⁾. This observational period may not be necessary if the child is at or past Tanner stage III (breast), particularly with advanced skeletal maturation⁸⁾.

2. Hormonal criteria

When the patient is suspected of having precocious puberty on the basis of clinical manifestations, the next steps for confirming the diagnosis include obtaining measurements of estradiol or testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) by high sensitivity-specificity assays. These assays should have a

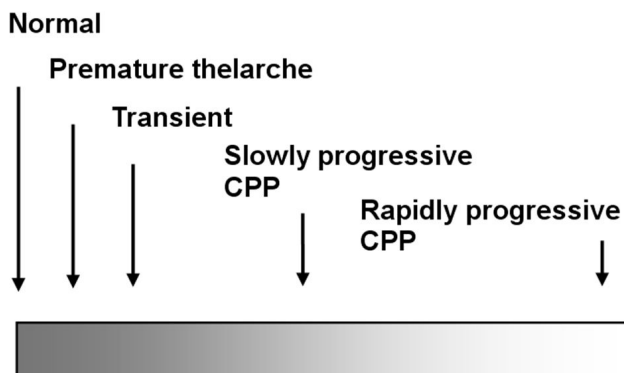


Fig. 1. The spectrum of precocious pubertal development ranges from normal variant or transient form to slowly progressive or rapidly progressive form.

sensitivity of at least 10 pg/mL for estradiol, 10 ng/dL for testosterone, and 0.2 IU/L for LH and FSH.

Determination of LH in the serum is the most valuable test in the diagnosis of CPP. A basal LH higher than 0.2 IU/L suggests evidence of the maturity of the HPG axis. However, about 53.8% of girls with Tanner stage II have levels in the prepubertal range, indicating the need for the GnRH stimulation test to establish the precise diagnosis⁹⁾. The GnRH stimulation test can be performed by administration of GnRH (serial samples at 30 minutes interval for 120 minutes after 100 µg intravenous infusion) or a GnRHa such as aqueous leuprolide (single sample at 60 minutes). Although peak LH levels show an overlap between prepubertal and early pubertal children, a prepubertal limit of peak LH at 3.3 to 5.0 IU/L has been suggested^{9, 10)}. According to the Health Insurance Review and Assessment Service of Korea, a peak LH higher than 5.0 IU/L can be considered a pubertal range. In contrast, FSH levels are not helpful diagnostically. However, the measurements of the LH/FSH ratio after GnRH stimulation may help to differentiate progressive CPP from nonprogressive variants.

Daytime estradiol concentration levels higher than 10 pg/mL in girls or testosterone levels higher than 25 ng/dL in boys represent pubertal conditions¹¹⁾. However, the serum level of sex hormone may be fluctuating in the early pubertal period or in the normal cyclic fashion of CPP.

3. Brain magnetic resonance imaging

Unsuspected intracranial organic lesions in CPP have been reported in 8% of girls and 40% of boys^{12, 13)}. Our study showed that 10.7% of girls and 42.8% of boys with CPP had intracranial pathology³⁾. The incidence of intracranial pathology with CPP decreases with age^{12, 13)}. Magnetic resonance imaging of the sella is indicated in all boys with CPP, girls less than 6 years of age with CPP, girls with rapidly progressive CPP, or neurologic findings.

4. Pelvic ultrasonography

Pelvic ultrasonography is helpful for differentiating CPP from premature thelarche. Girls with CPP have an increased uterine length (more than 3.4–4.0 cm) and ovarian volume (more than 1–3 mL) relative to girls in prepubertal period or with premature thelarche^{14, 15)}. Pelvic ultrasonography is also indicated to rule out abdominal or pelvic masses when pseudoprecocious puberty is suspected.

Management of CPP

1. Indication for GnRHAs

Generally accepted indications for administration of GnRHAs include complete and progressive CPP and compromised height potential, deterioration of final adult height prediction, or expectations of abnormal psychosocial behavior (Table 1)⁵⁾. From these criteria, it is obvious that careful follow-up examination should be made before a decision regarding the indication for treatment.

2. Currently available GnRHAs

GnRH agonistic analogs were developed throughout the 1970s and 1980s and were first applied in the management of CPP patients in 1981^{16, 17)}. GnRHAs suppress the serum levels of LH, FSH and sex steroids within 2–4 weeks by continuous stimulation of the pituitary gland, which leads to downregulation of GnRH receptors and desensitization of pituitary gonadotrophs. Several preparations of GnRHAs are currently available and are mostly effective. Leuprorelin, triptorelin, and goserelin can be used as monthly and quarterly depot preparations. Histrelin is available as a 12-month implant but currently only in the U.S. Short-acting preparations administered 1–3 times per day by nasal spray are also available. The depot preparations are preferred because of good compliance and convenience. A monthly depot preparation is typically used for most children with CPP. Table 2 indicates all depot preparations available in the Korean market, but only 3.75 mg formulations of leuprolide (all brands) and triptorelin (only decapeptyl) have been approved by the Korea Food and Drug Administration as therapeutic agents for the treatment of CPP. Recently, the quarterly regimen has been reported to be effective for suppression of the HPG axis^{18, 19)}, but a

Table 1. Suggested Indications for GnRHAs

1. Complete precocious puberty
2. Pubertal LH level after GnRH stimulation test above diagnostic limit (5.0 IU/L)
3. Rapid pubertal development
4. Abnormal height potential or
5. Loss of height potential during follow-up and/or
6. Psychosocial/behavioural reasons

randomized comparative study has not yet been conducted.

3. Dose of GnRHAs

The choice of the optimal dose of GnRHAs at the start of treatment is controversial. A study in Japan, where leuprolide was first developed, recommended a dose of more than 30 µg/kg to suppress gonadotropins²⁰⁾. In the U.S. it is presently recommended to administer 7.5 mg (or 200–300 µg/kg) of leuprolide acetate per month subcutaneously or intramuscularly. In Europe, the dose is 3.75 mg (or 150 µg/kg)²¹⁾. Most pediatric endocrinologists in Korea use 3.75 mg of leuprolide or triptorelin per month as a starting dose. More frequent injections or higher doses may be required in cases with improper suppression of the HPG axis.

4. Monitoring during treatment

Regular check-ups are recommended for monitoring the adequacy and efficacy of the treatment. Measurements of height, weight, growth velocity, and progression of puberty by the Tanner staging method²²⁾ should be made during each visit. It is also recommended that measurements be obtained for bone age, basal sex steroid, LH, FSH, and stimulated LH (using GnRH, aqueous GnRHAs, or the GnRHAs-containing depot preparations) in order to monitor the proper suppression of hormones within the first 3 months of treatment and every 6 months thereafter. If there is a progression of breast size, testicular enlargement, marked decreased growth velocity, or rapid bone age advancement, a prompt reassessment should be conducted. Bone age can be used to predict the final adult height during treatment by the Bayley–Pinneau method²³⁾. Treatment is considered adequate if the estradiol level becomes prepubertal²⁴⁾ or if the peak LH is below 2.3 IU/L after a classical GnRH test or below 6.6 IU/L 2 hours after administration of depot

Table 2. Depot GnRHAs Preparations in Korea

Depot preparation	Brand name	Dose
Leuprolide	Leuplin	3.75 mg, 11.25 mg
	Lucrin	3.75 mg, 11.25 mg
	Lorelin	3.75 mg, 11.25 mg
Triptorelin	Luphere	3.75 mg
	Decapeptyl	3.75 mg
Goserelin	Diphereline	3.75 mg, 11.25 mg
	Zoladex	3.6 mg, 10.8 mg
Buserelin	Superfact	5.775 mg
Histrelin	Supprelin	50 mg

leuprolide²⁵⁾.

5. Discontinuation of GnRHAs

The decision to discontinue GnRHAs treatment depends upon the primary goals of therapy, which may include prevention of short adult height, decreasing psychosocial distress, and facilitation of care of the developmentally delayed child⁶⁾. In terms of improving the height potential of girls, discontinuation of the therapy at the chronological age of 11 years²⁶⁾ or bone age of 12.0–12.5 years of age²⁷⁾ is generally suggested. However, bone age is not an appropriate single variable because it is unreliable as a predictor of height gain after treatment²⁸⁾.

6. Therapeutic agents that can be combined with GnRHAs

Growth hormone (GH) can be added if the growth velocity falls below the prepubertal normal range during treatment or if patients had begun treatment at a relatively late stage. Treatment with GH increases adult height relative to administration of GnRHAs alone in patients with CPP and slow growth velocity. Adjunctive therapies such as estrogen receptor blockers, aromatase inhibitors, antiandrogens, sex steroids, or nonaromatizable anabolic steroids may improve adult height, but require validation for safety by further studies⁸⁾.

7. Adverse reactions

Administration of GnRHAs produces relatively minimal adverse reactions. Headaches and menopausal symptoms such as hot flashes may be associated with therapy. Local complications, including sterile abscess, occur in 10% to 15% of patients¹⁸⁾. Although there is a concern about the possible risks of obesity and osteoporosis during and after treatment, longitudinal studies showed that GnRHAs do not increase the incidence of obesity or osteoporosis^{29–31)}.

8. Effect of GnRHAs treatment on final height

GnRHAs have been used in the treatment of CPP for more than 25 years, but there are no randomized controlled studies to estimate the effect of GnRHAs treatment on final height compared with untreated controls. The outcome of GnRHAs treatment on final height can only be evaluated by comparing the final height in treated patients with historical data from untreated patients. GnRHAs treatment has been reported to induce a height gain above the pretreatment height prediction of about 1.4 cm for each year of therapy

³²⁾. When GH is added, height gain can be increased to 2.0 cm above the pretreatment height prediction for each year of therapy³³⁾.

9. Long-term outcome after GnRHAs treatment

Long-term studies have reported that gonadal function is reactivated soon after cessation of treatment. The mean time for onset of menstruation after discontinuation of therapy is 16 months (range 2–61 months)³¹⁾. A regular ovarian cycle occurred in 60% to 96% of the patients, which is compatible with the normal pattern of menses at this age. Infertility has not been reported. There is no evidence that CPP increases the risk of hirsutism and/or polycystic ovary syndrome relative to the normal population³⁴⁾. Only limited studies are available on the effects of psychosocial development after GnRHAs treatment³⁵⁾. Further studies that employ standardized tools are needed.

GnRHAs treatment in conditions other than CPP

1. GnRHAs treatment in early puberty

Early puberty in girls is defined as onset of puberty at an age of 8–9 years. Some patients with early puberty may experience attenuated height potential and psychosocial problems³⁶⁾. However, routine use of GnRHAs in early puberty is not suggested because the effect of GnRHAs on final height is equivocal and because of the possibility of additional adverse effects³⁶⁾. GnRHAs therapy in early puberty should be restricted to patients for whom a dramatic decrease in height is predicted. This therapy should be conducted over a 6-month follow-up period for the advanced and rapidly progressive forms³⁷⁾.

2. GnRHAs treatment in GH deficiency or idiopathic short stature

Retrospective and prospective studies evaluating the effect of administering GnRHAs with GH in patients with GH deficiency or idiopathic short stature have provided controversial results^{38–40)}. Combined therapy with GnRHAs and GH in patients with GH deficiency or idiopathic short stature is not presently suggested⁸⁾.

Conclusion

GnRHAs therapy is the standard treatment modality for

CPP. The efficacy of treatment on final height is definite only in rapidly progressive CPP. Careful follow-up examination is recommended for 3–6 months to determine the rate of progression before a decision is made regarding treatment. This observational period may not be necessary if the patient is at or past Tanner stage III with advanced bone age. A monthly depot preparation is effective for suppressing the HPG axis and represents the treatment of choice in most children with CPP. Reverse reactions are of minor severity and acceptable. There is no evidence that GnRHAs causes obesity, osteoporosis, or severe long-term sequelae that lead to infertility. GnRHAs treatment for conditions other than CPP is not recommended.

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