ACTA BIOMED 2005; 76; 73-78

REVIEW

Combined therapy with Luteinizing Hormone Releasing Hormone agonist (LHRHa) and Growth Hormone (GH) in central precocious puberty

Cecilia Volta, Carla Regazzi, Juliette Ndaka, Rosa Vitale, Sergio Bernasconi
Department of Pediatrics University of Parma, Parma, Italy

Abstract. Luteinizing Hormone Releasing Hormone analogues (LHRHa) are considered the treatment of choice in central precocious puberty (CPP). Final height after therapy is usually higher than the predicted one before treatment, but about 60% of patients do not reach their genetic target. The association of Growth Hormone (GH) with LHRHa could be useful in a subgroup of children with CPP and low growth velocity in order to obtain a higher final height with a complete expression of genetic potential. Moreover, in children with early puberty adopted from developing countries, predicted adult height is significantly greater when the combined therapy, GH and LHRHa, is employed. In this paper the rationale for adding GH to LHRHa is discussed and the clinical reports from the literature are presented.

Key words: central precocious puberty, growth hormone, LHRH analogues

Definition of puberty and precocious puberty

Puberty is the transition period from childhood to adulthood. It is characterized by the appearance of secondary sexual characteristics and by the attainment of reproductive capacity. Other events such as growth spurt and bone age progression occur during puberty. The progression of sexual development is physiologically determined by the increase of pulsatile LHRH secretion from the hypothalamus and, consequently, by LH and FSH release from the pituitary gland. LH and FSH finally reach the testicular or ovarian tissue where they induce sexual hormone release.

Precocious puberty is usually defined as the appearance of secondary sexual characteristics before the age of 8 years in girls (thelarche before 8th birthday or menarche before 10th birthday) and before the age of 9 years in boys (testicular volume >4 ml or pubic hair appearance before the 9th birthday). These age limits, however, are somewhat arbitrary and might change with time (1).

Precocious puberty is central, or LHRH dependent, when determined by hypotalamic-pituitary-gonadal axis activation. On the contrary, in LHRH independent or pseudo precocious puberty the increase in sex hormones is secondary to primary gonadic activation.

There are three different types of gonadotropin dependent precocious puberty: central idiopathic precocious puberty (PP), organic central PP, PP due to ectopic gonadotropin secretion.

Central idiopathic PP (CPP) is the most frequent form; it can be familial and affects mostly girls (F: M = 10:1). Organic central PP is determined by central nervous system lesions such as cerebral tumours, arachnoid cysts, or by central nervous system damage like cranial trauma and neonatal asphyxia. Very rarely, precocious puberty can also be the result of ectopic gonadotropin secretion from malignant tumours (hepatoblastoma, chorionepithelioma, dysembryoma, etc).

In this review we will consider only idiopathic central precocious puberty, which is a continuum of

clinical presentations with different rates of progression. The spectrum of clinical forms ranges from premature telarche, transient PP, slowly or rapidly progressive PP (2, 3). Clinical follow-up is the only way to establish the strategy of treatment.

Indications to treatment in precocious puberty

The treatment in CPP is still under debate: it seems clear that not all patients need therapy.

Precocious puberty, however, can produce some undesirable psychosocial/behavioural and/or auxological effects that indicate treatment.

Some girls with precocious puberty could be at risk of premature sexual activity and, consequently, of early pregnancy; also the risk of sexual abuse, in particular in mentally retarded girls has to be considered. Behavioural disturbances include drug-alcohol dependence and low socio-cultural outcome (4).

From the auxological point of view, girls with precocious puberty might experience a deterioration of final height because of rapid bone maturation determined by sexual hormones, with final heights 4-9 cm lower than the genetic target and altered body proportions due to the greater growth of the spine compared with that of the limbs (5).

Treatment of precocious puberty

LHRHa are considered the treatment of choice in CPP. They cause desensitization and down-regulation of LHRH receptors and therefore prevent the physiological stimulus of LHRH on gonadotropin secretion from the pituitary gland. There are many different commercial forms of these drugs; the most used are LHRHa depot. Depot analogues (like Triptorelin or Leuprorelin) are administered via subcutaneous or intramuscular injection once in 3-4 weeks and their use is clearly better accepted by the patients. Moreover, subcutaneous administration is less painful for the patient than the intramuscular one.

Depot LHRHa suppress hypothalamus-pituitary-gonadal axis, induce regression of secondary sexual characteristics, and improve growth potential and final height. Final height after therapy is usually higher than the predicted one before treatment. In Table 1 final heights of treated girls from the most recent data are reported. Briefly 75% of the patients will reach their genetic target height range and 40% of them will reach their genetic target. Treatment outcome is influenced by many factors and is more effective if it is used in younger patients, if there is a short delay in the onset of treatment since the appearance of symptoms, if puberty is rapidly progressive, if it is used for a longer period of time, and if the predicted height is higher at the beginning of the therapy (6).

When treatment is stopped, its effect on hormonal secretion suppression is completely reversible and does not interfere with fertility (1).

The optimal duration of this therapy is still under discussion. Some criteria for interrupting the therapy are the achievement of a bone age > 12-13 years or of a stature equal to the predicted one or a poor compliance to treatment.

Adverse effects

After the first injection of depot LHRHa a short term increase in LH and sex steroid secretion (“flare-up phase”) appears and therefore transient vaginal withdrawal bleedings may occur in girls. In a small

Table 1. Final heights of girls with central precocious puberty after treatment with depot LHRHa

Reference	N.	Target height (cm)	Predicted height (cm)	Final height (cm)
Arrigo (19)	71	161.5	155.5	158.8
Mul (20)	87	168.0	155.3	162.5
Heger (21)	50	163.6	154.8	160.6
Kauli (5)	48	157.7	154.4	159.6
Galluzzi (22)	22	163.5	155.2	158.5
Klein (6)	80	163.7	149.3	159.8

group of patients bleedings can go on. Sometimes minor menopausal symptoms such as depression, nausea, hot flushes can appear.

There are no randomized studies concerning long-term adverse effects. The most controversial topic is the effect of depot LHRHa on bone mineralization. Partsch et al. (1) exclude a role of this treatment in bone mass reduction while Antoniazzi (7) advises an oral supplementation of calcium in order to prevent this possibility.

GnRHa and GH combined therapy

Rationale for the combination treatment

In CPP GH and IGF1 secretion clearly increases. This event depends on estrogen secretion and causes the growth spurt. Studies concerning the effect of treatment with LHRHa on the GH-IGF1 axis are few and partially discrepant (8).

Among patients with low height velocity (<4 cm/year or <25° pct for bone age) the spontaneous or stimulated secretion of GH or its urinary excretion were reduced in two studies, normal in another one; IGF1 levels were also widely variable. During therapy IGFBP3 levels are reported as unaffected or increased. The slow growth velocity in some patients could be secondary to an abnormal IGFBP3/IGF1 ratio with a secondary decrease in free IGF1. Therefore on this basis adding GH treatment to the LHRHa in this subgroup of children could be a logical procedure.

Clinical experiences

In 1991 Oostdijk et al. (9) associated GH to LHRHa in 3 girls with precocious puberty and low height velocity, obtaining an improvement of predicted heights after 18 months of treatment. Since then other 4 studies have addressed the subject, whose main results are reported in table 2.

Saggese et al. in 1995 (10) evaluated twelve girls with CPP who had been treated with depot triptorelin for about 2 years and showed a low growth velocity (3±0.9 cm/yr); 4 out of the 12 patients had abnormal mean spontaneous secretion of GH and 2 out of 7 had abnormal mean stimulated GH levels. At the beginning of the study, all patients were treated with GH at a dose of 0.6 IU/kg. After one year of associated therapy their mean growth velocity increased to 6±1.3 cm/year and the predicted height improved from -1.7±0.6 SDS to 1.0±0.6 SDS. No data on final height were available and no control group was present.

In 1995 Tatò et al. (11) evaluated 30 girls with precocious puberty and a decrease of growth velocity below the 25th percentile during the first year of therapy with triptorelin. Fifteen patients were treated with the associated therapy GH-LHRHa while the control group continued with triptorelin alone. In the first group a significant increase in serum IGF1,

Table 2. Associated treatment in girls with CPP: clinical experiences

	N.	Treatment	Months of therapy	Outcomes
Saggese et al. (10)	12	GnRHa + GH (0,2 mg/kg/wk)	12	GV increment of 3 cm/y PAH increment of 2.7 SDS
Tatò et al. (11)	30	15 GnRHa alone 15 GnRHa + GH (0.2 mg/kg/wk)	12	GV increment of 4 cm/y in the case group
Pasquino et al. (12)	20	10 GnRHa alone 10 GnRHa + GH (0.3 mg/kg/wk)	24-48	FH > 7.9±1.1 cm over PAH in the case group vs 1.6±1.2 cm in the control group.
Pasquino et al. (13)	35	18 GnRHa alone 17 GnRHa + GH (0.3 mg/kg/wk)	24-48	FH > 8.2±4.8 cm over PAH in the case group vs 2.3±2.9 cm in the control group

GV = growth velocity; PAH = predicted adult height; FH = final height

IGFBP3 and urinary GH levels after 12 months of associated therapy was present; the growth velocity was higher than that of the control group and also higher than that presented before the association of GH in the therapy. The AA. suggest that the association of GH might be necessary in patients with precocious puberty treated with LHRHa in which a significant decrease of growth velocity is present.

Pasquino et al. published a similar case-control study: 10 girls were treated with LHRHa alone and 10 girls were treated with the associated therapy GH-LHRHa (12). This study started after 3 years of therapy with LHRHa in the whole group with CPP, whose growth velocity decreased below the 25th centile for chronological age and with no improvement in predicted adult height. All patients had a normal GH secretory status as demonstrated by GH stimulation tests and evaluation of spontaneous GH secretion. Auxological data were evaluated at the beginning of treatment and every six months. The results were: 1) plasma LH and FSH peaks after LHRH test were equally suppressed in both groups; 2) bone age progressed with the same velocity in the two groups; 3) ovarian volume and uterine length were modified in a comparable way in the two groups; 4) subsequent menses were regular without no difference between the two groups after the interruption of therapy. However, in the case group adult height was significantly higher than the predicted pre-treatment one and the target height was significantly exceeded. In the group treated with GH-LHRHa a gain of 7.9 cm in adult height was obtained, compared to the figure of 1.6 cm in the control group.

Recently the same AA. reported a nearly doubled number of patients on combination treatment and the results were confirmed (13). The LHRHa and GH treated group showed a mean increase of 8.2 cm. over their predicted height at the beginning of treatment compared to the 2.3 cm. figure of the LHRHa treated group. The final height of the first group was 161.2 cm, while that of the control group was 156.6 cm.

Briefly, the association of therapy with GH and LHRHa could be useful in a subgroup of girls with CPP, low growth velocity and impaired predicted height in order to obtain a higher final height with a complete expression of genetic potential. None of these studies reported adverse effects of the associated treatment, even though the number of treated patients is rather small.

GH and GnRHa associated therapy in adopted children

Early onset of puberty is more frequent in children adopted from developing countries probably in relation to a better lifestyle and to the improvement of nutritional status. This is possibly favoured by an increase of leptin secretion acting as a permissive factor for the onset of puberty (14).

Treatment with LHRHa is frequently necessary, but the results are not encouraging due to the significant decrease of growth velocity (15).

Tuvemo et al have studied a group of 46 girls coming from India, Sri Lanka, Indonesia, Colombia and Peru with a mean age of 8.3 yrs at the beginning of treatment (16). In this randomized study, 22 girls were treated with LHRHa alone and 24 with associated therapy GH-LHRHa. After 2 years of treatment,

Table 3. Associated treatment in adopted children: clinical experiences

	N.	Treatment	Months of therapy	Outcomes
Tuvemo et al. (16)	46 F	22 GnRHa alone 24 GnRHa + GH (0.2 mg/kg/wk)	24	GV increment of 3.7 cm/2yrs vs controls PAH increment of 1.8 cm in the case group vs decrement of 0.9 cm in controls
Mul et al. (17)	30 3 M, 27 F	16 GnRHa alone 14 GnRHa + GH (1.33 mg/m^2/day)	36	GV increment of 2.7 cm/3yrs vs controls PAH increment of 10.1 cm in the case group vs. 5.7 cm in controls

GV = growth velocity; PAH = predicted adult height

growth velocity was significantly increased in the group treated with the combined therapy as well as predicted adult height and no significant difference was found in the increase in mean skeletal maturity between the two treatment groups. Moreover no adverse effects of the associated therapy such as an increase of BMI, polycystic ovaries or interference in glucose metabolism were reported.

In 2001 Mul et al. published the results of a 3-year prospective randomized trial which included 30 adopted children (27 girls and 3 boys) with early puberty coming from India, Sri Lanka, Colombia and South Korea (17). The first group (A) was treated with LHRHa alone and the other (B) with the associated therapy. Height velocity in the first year of therapy was 5.4 and 6.7 cm/y respectively in group A and B; subsequently, it decreased but continued to be higher in group B at any time point. No significant difference between the rates of bone maturation in both treatment groups was observed.

Of course no definite conclusions can be drawn from these studies; in fact final heights were not reached yet, target heights were unknown, as it usually happens in adopted children, and predicted height was calculated based on bone age evaluation by western standards.

Conclusions

Despite the encouraging results described up to now, it appears that it is necessary to better identify patients, both on clinical and laboratory grounds, who could really benefit from this therapy.

It is, in fact, questionable to employ such expensive and stressful treatment in order to obtain heights above the target heights (18).

For these reasons the combined treatment GH and LHRHa in CPP is still experimental and should be employed only within randomized controlled studies.

References

1. Partsh CJ, Hager S, Sippel WG. Management and outcome of central precocious puberty. *Clin Endocrinol* 2002; 56: 129-48.
2. Kelnar JH, Stanhope R. Height prognosis in girls with central precocious puberty treated with GnRH analogues. *Clin Endocrinol* 2002; 56: 295-6.
3. Volta C, Bernasconi S, Cisternino M, et al. Isolated premature thelarche and thelarche variant: clinical and auxological follow-up of 119 girls. *J Endocrinol Invest* 1998; 21: 180-3.
4. Ehrhardt AA, Meyer-Bahlburg HFL. Idiopathic precocious puberty in girls: long-term effects on adolescent behaviour. *Acta Endocrinol* 1986; 279 (Suppl): 247-53.
5. Kauli R, Galatzer A, Kornreich L, Lazar R, Pertzelan A, Laron Z. Final height of girls with central precocious puberty, untreated versus treated with cyproterone acetate or GnRH analogue. A comparative study with re-evaluation of predictions by the Bayley-Pinneau method. *Horm Res* 1997; 47: 54-61.
6. Klein KO, Barnes K, Jones JV, Feuillan PP, Cutler GB. Increased final height in precocious puberty after long-term treatment with LHRH analogues: the National Institutes of Health Experience. *J Clin Endocrinol Metab* 2001; 86: 4711-6.
7. Antoniazzi F, Bertoldo F, Lauriola S, et al. Prevention of bone demineralization by calcium supplementation in precocious puberty during gonadotropin-releasing hormone agonist treatment. *J Clin Endocrinol Metab* 1999; 84: 1992-6.
8. Walvoord EC, Pescovitz OH. Combined use of growth hormone and gonadotropin releasing hormone analogues in precocious puberty: theoretic and practical considerations. *Pediatrics* 1999; 104: 1010-4.
9. OOstdijk W, Drop SLS, Odink RJH, Hummelink R, Partsch CJ, Sippel WG. Long-term results with a slow-release gonadotropin-releasing hormone agonist in central precocious puberty. *Acta Paediatr Scand* (Suppl) 1991; 372: 39-45.
10. Saggese G, Pasquino AM, Bertelloni S, et al. Effect of combined treatment with gonadotropin releasing analogue and growth hormone in patients with precocious puberty who had subnormal growth velocity and impaired height prognosis. *Acta Paediatr* 1995; 84: 299-304.
11. Tatò L, Saggese G, Cavallo L, et al. Use of combined GnRH agonist and hGH therapy for better attaining the goals in precocious puberty treatment. *Horm Res* 1995; 44 (Suppl 3): 49-54.
12. Pasquino AM, Pucarelli I, Segni M, Matrunola M, Cerrone F. Adult height in girls with central precocious puberty treated with gonadotropin-releasing hormone analogues and growth hormone. *J Clin Endocrinol Metab* 1999; 84: 449-52.
13. Pucarelli I, Segni M, Ortore M, Arcadi E, Pasquino AM. Effects of combined gonadotropin-releasing hormone agonist and growth hormone therapy on adult height in precocious puberty: a further contribution. *J Pediatr Endocrinol Metab* 2003; 16: 1005-10.
14. Hileman SM, Pierroz DD, Flier JS. Leptin, nutrition, and reproduction: timing is everything. *J Clin Endocrinol Metab* 2000; 85: 804-7.

15. Virdis R, Street ME, Zampolli M, et al. Precocious puberty in girls adopted from developing countries. *Arch Disease in Childhood* 1998; *78*: 152-4.
16. Tuvemo T, Gustafsson J, Proos LA and the Swedish growth Hormone Advisory Group. Growth hormone treatment during suppression of early puberty in adopted girls. *Acta Paediatr* 1999; 88: 929-32.
17. Mul D, Oostdijk W, Waelkens JJJ, Schulpen TWJ, Drop SLS. Gonadotropin releasing hormone agonist treatment with or without recombinant human GH in adopted children with early puberty. *Clin Endocrinol* 2001; 55: 121-9.
18. Lee PA. The effects of manipulation of puberty on growth. *Horm Res* 2003; 60 (Suppl 1): 60-7.
19. Arrigo T, Cisternino M, Galluzzi F, Bertelloni S, Pasquino AM, Antoniazzi F. Analysis of the factors affecting auxological response to GnRH agonist treatment and final height outcome in girls with idiopathic central precocious puberty. *J Endocrinol* 1999; 141: 140-4.
20. Mul D, Oostdijk W, Otten BJ, et al: Final height after gonadotropin-releasing hormone agonist treatment for central precocious puberty. *J Pediatr Endocrinol Metab* 2000; 13: 765-72.
21. Heger S, Partsch C, Sippell WG. Long term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportion, bone mineral density, and reproductive function. *J Clin Endocrinol Metab* 1999; 84: 4583-90.
22. Galluzzi F, Salti R, Bindi G, Pasquini E, La Cauza C. Adult height comparison between boys and girls with precocious puberty after long-term gonadotropin-releasing hormone analogue therapy. *Acta Paediatr* 1998; 87: 521-7.

Accepted in original form: 25 May 2005
Correspondence: Cecilia Volta, MD
Dipartimento Età Evolutiva
Via Gramsci 14
43100 Parma
Tel. 0521/702723
Fax 0521/290460
E-mail: cecivolt@unipr.it