

# Randomised trial of LHRH analogue treatment on final height in girls with onset of puberty aged 7.5-8.5 years

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## Abstract

**Objective**—To study the effectiveness of luteinising hormone releasing hormone (LHRH) analogues in improving final height in girls affected by early puberty.

**Patients**—Forty six consecutive girls with onset of puberty aged 7.5-8.5 years randomly divided into two groups: one treated with 3.75 mg triptorelin intramuscularly every four weeks (group 1); and the other with no treatment (group 2).

**Results**—Mean (SD) chronological age at onset of menarche was significantly higher in group 1 than in group 2 (11.9 (1.0) v 10.8 (0.7) years). However, mean (SD) height at menarche (152.7 (7.2) v 152.5 (5.7) cm) and mean (SD) growth after menarche (4.9 (3.0) v 5.4 (2.2) cm) were similar in both groups. The mean (SD) final height was similar in the two groups (group 1, 158.1 (6.2) cm; group 2, 158.6 (6.0) cm) and not significantly different from target height. Fourteen of 20 patients in group 1 and 12 of 18 patients in group 2 showed final height equal to or higher than target height. Final heights of girls with poor initial height prognosis were significantly lower than those of girls with good prognosis, but in patients with the same initial height prognosis, both groups showed final heights similar and not significantly different from their target heights.

**Conclusions**—LHRH analogue has no apparent effect on final height in subjects with onset of puberty between 7.5 and 8.5 years.

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Since their synthesis in 1980, the superactive luteinising hormone releasing hormone (LHRH) analogues have been widely used as therapeutic agents, quickly becoming the treatment of choice in central precocious puberty.<sup>1</sup> The progestational agents used in the past were not very effective in improving final height,<sup>2,3</sup> whereas the results of preliminary studies with LHRH analogues showed a significant improvement in height predictions during treatment.<sup>4-6</sup> These first favourable results might have aroused too much enthusiasm in physicians, leading to a potential risk of "overprescription".<sup>7</sup>

In more recent years, long term studies have produced differing results, with considerable variability in final heights for both treated and untreated patients.<sup>8-13</sup> It has been suggested that LHRH analogue treatment is not equally efficacious in all cases and that the final adult height potential could be attained without treatment in those individuals with central precocious puberty who have a good initial height prognosis.<sup>13-18</sup>

One of the most frequent variants in the spectrum of central precocious puberty is so called early puberty, with a pubertal onset only mildly in advance of normal.<sup>19</sup> The management of early puberty is a common problem for paediatricians. However, to our knowledge no specific data are available on the effectiveness of LHRH analogues in improving final height in these children.

Therefore, we examined 46 girls referred to us because of early puberty and divided them randomly into two groups, one treated with triptorelin and the other followed without treatment.

## Methods

### PATIENTS

Forty six girls referred for early puberty were examined. The inclusion criteria for the study were breast development between 7.5 and 8.5 years (mean (SD) chronological age, 7.7 (0.5) years), bone age advancement, and height velocity (evaluated three to six months before)  $\geq 1.5$  SD score, in the absence of associated defects that could affect final height, such as growth hormone deficiency or congenital adrenal hyperplasia. Girls with learning disability and pathology such as shunted hydrocephalus or cerebral palsy were also excluded. Magnetic resonance imaging of the pituitary gland and pelvic ultrasound were performed to exclude organic pathologies. Our study was approved by the ethics committee of the hospital and written informed parental consent was obtained before the start of our study. The 46 consecutive patients were assigned randomly to group 1 or group 2 alternately. Patients in group 1 (n = 23) were treated with triptorelin (D-Trp6-LHRH) depot (3.75 mg every four weeks by intramuscular injection); patients in group 2 (n = 23) had the same follow up, but without treatment. Two patients from group 2 were lost to follow up after the first examination and were excluded from our study.

In group 1, treatment with triptorelin was carried out for a mean of 25 months (range, 12-40) and was discontinued at a mean (SD)

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Table 1 Auxological findings in the two groups at the first examination

	Group 1	Group 2
Number	23	21
Chronological age (years)	8.5 (0.6)	8.4 (0.5)
Bone age (years)	10.6 (0.8)	10.3 (0.6)
Height (cm)	134.9 (6.8)	135.5 (5.9)
Target height (cm)	158.0 (7.6)	158.8 (3.9)

Values are mean (SD).

chronological age of 10.6 (0.8) years (range, 9.3–12.4) and bone age of 12.4 (0.9) years (range, 9.8–13.5). The time of discontinuation was individualised, based on bone age and growth rate during the last course of treatment and on the wishes of the girl and her family. After treatment was discontinued, the patients were followed up for a mean of 33 months (range, 16–69), with 20 patients reaching adult height. The patients from group 2 were followed up for a mean of 41 months (range, 31–81), with 18 patients reaching adult height. All the girls were evaluated at six month intervals during the first year, then every year; the girls from group 1 were evaluated again when treatment was discontinued.

#### GROWTH EVALUATION

At each examination the following were evaluated: height (mean of three measurements) with a Harpenden stadiometer,<sup>20</sup> pubertal staging according to Tanner,<sup>21</sup> bone age (single observer) with the atlas of Greulich and Pyle,<sup>22</sup> and predicted height calculated by the method of Bayley and Pinneau, which has been found to be the most accurate method for patients with precocious puberty.<sup>23</sup>

Target height was defined as the corrected midparental height for each patient and was calculated according to Tanner *et al.*<sup>24</sup>

Final adult height was defined as growth of < 0.3 cm in a period greater than six months associated with complete or near complete epiphyseal fusion.<sup>10</sup>

Good or poor initial height prognosis was determined in all the patients according to the following criteria: (1) bone age advance over chronological age less or more than 18 months; (2) height age/bone age more or less than 0.9.<sup>17</sup>

All girls from group 1 complied well, as assessed at each examination by history, growth rate, progression of pubertal signs, and the plasma gonadotrophin response to gonadorelin. Drug safety monitoring included routine measurement of hepatic, renal, and haematological functions, thyroid hormone, and prolactin concentrations.

Table 3 Final and target heights in the two groups of girls

	n	Final height (cm)	Target height (cm)
Group 1	20	158.1 (6.2)	157.0 (5.2)
Group 2	18	158.6 (6.0)	158.5 (4.2)

Values are mean (SD).

#### STATISTICAL ANALYSIS

All results were expressed as mean (SD), unless indicated otherwise. We used a parametric statistical analysis; the variables not normally distributed were evaluated after logarithmic transformation. The results were analysed with variance analysis for repeated measurements, paired *t* test, and Student's *t* test. Multiple linear regression and the *r* correlation coefficient were also calculated. A power calculation to determine how many patients were needed to show a significant difference was done by the power pattern for a significance of 0.05 for the *t* test and for the main parameters that we considered. The values obtained were ~ 20 subjects for each group for a power of the test always higher than 80%.

#### Results

Table 1 reports the measurements taken at the first examination in the two groups of patients: chronological age, bone age, height, and target height were similar in the two groups. During 24 months of follow up, the height SD score for bone age, predicted height, bone age/chronological age ratio, and bone age SD score did not change significantly in the two groups. Significant breast development was seen only in group 1, whereas height velocity decreased in both groups, although more significantly in group 1 (table 2). Chronological age at onset of menarche was significantly higher in group 1 than in group 2 (11.9 (1.0) *v* 10.8 (0.7) years; *p* < 0.005); height at menarche (152.7 (7.2) *v* 152.5 (5.7) cm), and growth after menarche (4.9 (3.0) *v* 5.4 (2.2) cm) were similar in both groups. The mean final height was similar in the two groups and not significantly different from target height (table 3). Fourteen of 20 patients in group 1 and 12 of 18 cases in group 2 had a final height equal to or higher than target height. In both groups there was a significant positive correlation between adult final height and height at first examination and target height (*p* < 0.005).

Table 4 shows final heights of patients of both groups subdivided according to height prognosis at onset. Final heights of girls with poor initial height prognosis were significantly

Table 2 Breast stage according to Tanner, bone age SD score, bone age/chronological age ratio, predicted adult height, height SD score for bone age (SDS<sub>BA</sub>), and height velocity evaluated in the two groups of girls at onset of puberty and after 24 months of follow up

	n	Breast stage		Bone age SD score		Bone age/chronological age		Predicted height (cm)		Height SDS <sub>BA</sub>		Height velocity (cm/year)	
		0	24 months	0	24 months	0	24 months	0	24 months	0	24 months	0	24 months
Group 1	21	2.2 (0.4)	2.5 (0.6)	2.1 (0.7)	1.8 (1.0)	1.2 (0.1)	1.2 (0.1)	157.8 (9.1)	159.6 (8.4)	-0.6 (1.1)	-0.8 (1.4)	10.5 (7.2)**	5.4 (1.4)
Group 2	21	2.3 (0.6)*	3.8 (0.9)	2.1 (0.5)	2.4 (1.0)	1.2 (0.1)	1.2 (0.1)	159.3 (5.4)	160.2 (5.6)	-0.4 (0.8)	-0.6 (1.0)	9.9 (2.4)***	6.9 (2.0)

Values are mean (SD).

\**p* < 0.001 compared with breast after 24 months; \*\**p* < 0.01 compared with height velocity after 24 months; \*\*\**p* < 0.05 compared with height velocity after 24 months.

Table 4 Final and target heights in the two groups of girls divided by height prognosis at onset

	Good prognosis			Poor prognosis		
	Total (n = 16)	Group 1 (n = 8)	Group 2 (n = 8)	Total (n = 22)	Group 1 (n = 12)	Group 2 (n = 10)
Final height (cm)	161.4 (4.5)*	162.2 (4.0)	161.0 (5.0)	156.0 (6.0)	155.4 (6.0)	156.8 (6.3)
Target height (cm)	158.7 (4.9)	158.9 (6.5)	158.6 (2.9)	156.9 (4.6)	155.6 (3.9)	158.0 (5.1)
Final ≥ target	15/16	8/8	7/8	11/22	6/12	5/10
Final > target	11/16	7/8	4/8	7/22	5/12	2/10

Values are mean (SD) where appropriate.

\*p < 0.005 compared with patients with poor prognosis.

lower than those of girls with good prognosis (p < 0.005; table 4); however, in patients with the same initial height prognosis, both groups showed similar final heights, not significantly different from their target heights. The percentages of patients with a final height equal to or higher than target height were not significantly different in the various groups. For patients with poor initial height prognosis, final height was higher than target height in only two of the 10 patients in group 2 and five of the 12 patients in group 1. However, this difference was not significant (table 4).

### Discussion

Some investigators have suggested that age at pubertal onset might be one of the factors affecting final adult height in central precocious puberty, sometimes independently from treatment.<sup>3 12 25–27</sup> Sigurjonsdottir and colleagues<sup>25</sup> and Murram *et al*,<sup>26</sup> in studies on spontaneous growth in untreated girls with central precocious puberty, reported that girls who started to develop before the age of 6 years were shorter than those who started after 6 years, and Schoevaart and colleagues<sup>3</sup> found good final heights in subjects with later pubertal onset. Kletter and Kelch<sup>11</sup> reported final adult height not significantly different in patients with pubertal onset at greater than 6 years of age, both untreated patients and those treated with LHRH analogues. Moreover, in all these studies, age at pubertal onset was only one of the factors of height variability in samples of patients that were not homogeneous with regard to sex, diagnosis, type of agonist used, pattern of controls, etc. To our knowledge, our results are the first to be published that derive from the study of a homogeneous population of girls affected exclusively by early puberty. Although a randomised study is the ideal method for assessing the auxological effectiveness of treatment, it might appear ethically questionable.<sup>27</sup> However, our study was extensively discussed and approved by the ethics committee of the hospital, it did not concern children in the first years of life, and the parents were specifically informed before obtaining their consent. They were also made aware of the controversies concerning the treatment that were a cause of uncertainty for paediatricians and anxiety for the family.

In agreement with Kletter and Kelch,<sup>11</sup> we found that the LHRH analogue had little effect on final height in subjects with early puberty; in fact, the auxological follow up and final heights of our patients were similar in the treated and untreated groups. However, in girls examined by Kletter *et al*, the mean final height remained

nearly 1 SD score below the mean target height, whereas we found that the final heights in 69% of patients were equal to or higher than target heights, and did not differ from the current mean adult height observed in the Emilia-Romagna region of Italy.<sup>28</sup>

Recent studies on large samples of the female population have shown in the past 20 years a trend towards earlier appearance of pubertal signs. This phenomenon does not appear to have a negative influence on adult height.<sup>29–32</sup> Herman-Giddens *et al*,<sup>29</sup> in a sample of 15 439 white American girls found that more than 15% began puberty between 7 and 8 years of age. The same authors observed also that the mean heights of the study girls were higher than a national sample of race specific data, collected ~ 20 years before. Therefore, they suggested that practitioners might need to revise their “historical” criteria for the diagnosis of precocious puberty.

Early puberty could be inserted in to this phenomenon of secular trend as a form with genetically fixed auxological features, and it could be defined as a “paraphysiological” condition. In agreement with this hypothesis, we observed in our patients that final height was significantly affected only by height at pubertal onset and by target height, characteristics that are also described in normal puberty,<sup>12</sup> and that treatment did not appear to improve the initial height prognosis. We must point out, however, that these results need confirmation; the small number of patients with poor prognosis at onset, in fact, could blunt positive results.

However, all authors agreed that the age of menarche, in the past 20 years, has remained unchanged, at ~ 12 years, although there are some slight ethnic differences. Marti-Henneberg and Vizmanos,<sup>30</sup> in a sample of 163 girls from north east Spain, found a negative correlation between pubertal onset and its duration, so they concluded that the duration of puberty in girls depended on the timing of its onset. In our study, the untreated girls showed a regular and fairly quick progression of pubertal signs and onset of menarche at a mean age of 10.8 years. However, we assume that these differences in pubertal development between our girls and those examined by Marti-Henneberg and Vizmanos might be determined by ethnic/genetic factors that did not affect the final height. In fact, in our experience, early puberty is associated with a satisfactory height prognosis that is not significantly modified by treatment, except perhaps in some selected cases. In addition, the observation that height at menarche was achieved at different times, but was similar in

the two groups, indicates a predetermined auxological destiny in subjects with early puberty, which is unaffected by treatment.

Finally, we have to point out that our study evaluated only the auxological results of LHRH analogue treatment. However, other factors might justify treatment and should be considered by paediatricians when deciding on treatment—for example, important emotional and cognitive difficulties that can sometimes affect girls with precocious pubertal development.

- 1 Crowley WF, Comite F, Vale WW, Rivier J, Loriaux DL, Cutler GB. Therapeutic use of pituitary desensitisation with a long acting agonist: a potential new treatment of precocious puberty. *J Clin Endocrinol Metab* 1981;52:370-2.
- 2 Sogro W, Kinaly E, Homoki J, et al. The effects of cyproterone acetate on skeletal growth in children with precocious puberty. *Acta Endocrinol (Copenh)* 1987;115:44-56.
- 3 Schoevaart CE, Drop SLS, Otten BJ, Slijper FME, Degenhart HJ. Growth analysis up to final height and psychosocial adjustment of treated and untreated patients with precocious puberty. *Horm Res* 1990;34:197-203.
- 4 Boepple PA, Mansfield MJ, Crawford JD, Crigler IF, Jr, Blizzard RM, Crowley WF, Jr. Gonadotropin-releasing hormone agonist treatment of central puberty: an analysis of growth data in a developmental context. *Acta Paediatr Scand Suppl* 1990;367:38-43.
- 5 Brauner R, Malandry F, Rappaport R. Predictive factors for the effect of gonadotrophin releasing hormone analogue therapy on the height of girls with idiopathic precocious puberty. *Eur J Pediatr* 1992;151:728-30.
- 6 Hummelink R, Oostdijk W, Partsch CJ, Odink RJ, Drop SL, Sippel WG. Growth, bone maturation, and height prediction after three years of therapy with the slow release GnRh-agonist decapeptyl depot in children with central precocious puberty. *Horm Metab Res* 1992;24:122-6.
- 7 Kreiter ML, Cara JF, Rosenfield RL. Modifying the outcome of complete precocious puberty: to treat or not to treat. In: Grave GD, Cutler GB, eds. *Sexual precocity*. New York: Raven Press, 1993:109-20.
- 8 Oerter KE, Manasco PK, Barnes KM, Jones J, Hill S, Cutler GB, Jr. Effects of luteinizing hormone-releasing hormone agonists on final height in luteinizing hormone-releasing hormone-dependent precocious puberty. *Acta Paediatr Suppl* 1993;388:62-8.
- 9 Antoniazzi F, Cisternino M, Nizzoli G, et al. Final height in girls with central precocious puberty: comparison of two different luteinizing hormone-releasing hormone agonist treatments. *Acta Paediatr* 1994;83:1052-6.
- 10 Cacciari E, Cassio A, Balsamo A, et al. Long-term follow-up and final height in girls with central precocious puberty treated with luteinizing hormone-releasing hormone analogue nasal spray. *Arch Pediatr Adolesc Med* 1994;148:1194-9.
- 11 Kletter GB, Kelch RP. Effects of gonadotropin-releasing hormone analog therapy on adult stature in precocious puberty. *J Clin Endocrinol Metab* 1994;79:331-4.
- 12 Oostdijk W, Rikken B, Schreuder S, et al. Final height in central precocious puberty after long term treatment with a slow release GnRh agonist. *Arch Dis Child* 1996;75:292-7.
- 13 Kauli R, Galatzer A, Kornreich L, Lazar L, Pertzalan A, Laron Z. Final height of girls with central precocious puberty, untreated versus treated with cyproterone acetate or GnRH analogue. *Horm Res* 1997;47:54-61.
- 14 Kreiter M, Burstein S, Rosenfield RL, et al. Preserving adult height potential in girls with idiopathic true precocious puberty. *J Pediatr* 1990;117:364-70.
- 15 Rosenfield RL. Selection of children with precocious puberty for treatment with gonadotropin releasing hormone analogs. *J Pediatr* 1994;124:989-91.
- 16 Brauner R, Adan L, Malandry F, Zantleifer D. Adult height in girls with idiopathic true precocious puberty. *J Clin Endocrinol Metab* 1994;79:415-20.
- 17 Ghirri P, Bottone U, Gasperi M, et al. Final height in girls with slowly progressive untreated central precocious puberty. *Gynecol Endocrinol* 1997;11:301-5.
- 18 Bassi F, Bartolini O, Neri AS, et al. Precocious puberty: auxological criteria discriminating different forms. *J Endocrinol Invest* 1994;17:793-7.
- 19 Stanhope R, Brook CGD. Disorders of puberty. In: Brook CGD, ed. *Clinical paediatric endocrinology*. Oxford: Blackwell, 1989:169-88.
- 20 Cameron N. The methods of auxological anthropometry. In: Falkner F, Tanner JM, eds. *Human growth: a comprehensive treatise*. 2nd ed. New York: Plenum Press, 1986:3-46.
- 21 Tanner JM. *Growth and adolescence*. 2nd ed. Oxford: Blackwell Publishers, 1962.
- 22 Greulich WW, Pyle EI. *Radiographic atlas of skeletal development of the hand and wrist*. 2nd ed. Stanford: Stanford University Press, 1966.
- 23 Bayley N, Pinneau S. Tables for predicting adult height from skeletal age: revised for use with Greulich-Pyle hand standards. *J Pediatr* 1952;40:423-41.
- 24 Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2-9 years allowing for height of parents. *Arch Dis Child* 1970;45:755-62.
- 25 Sigurjonsdottir TJ, Hayles AB. Precocious puberty. A report of 96 cases. *Am J Dis Child* 1968;115:309-21.
- 26 Murrain D, Dewhurst J, Grant DB. Precocious puberty: a follow-up study. *Arch Dis Child* 1984;59:77-8.
- 27 Paul D, Conte FA, Grumbach MM, Kaplan SL. Long term effect of gonadotropin-releasing hormone agonist therapy on final and near-final height in 26 children with true precocious puberty treated at a median age of less than 5 years. *J Clin Endocrinol Metab* 1995;80:546-51.
- 28 Cacciari E, Corazza GR, Salardi S, et al. What will be the adult height of coeliac patients? *Eur J Pediatr* 1991;150:407-9.
- 29 Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the pediatric research in office settings network. *Pediatrics* 1997;99:505-12.
- 30 Marti-Henneberg C, Vizmanos B. The duration of puberty in girls is related to the timing of its onset. *J Pediatr* 1997;131:618-21.
- 31 De La Puente ML, Canela J, Alvarez J, Salleras L, Vicens-Calvet E. Cross-sectional growth study of the child and adolescent population of Catalonia (Spain). *Ann Hum Biol* 1997;24:435-52.
- 32 Helm P, Groulund L. A halt in the secular trend towards earlier menarche in Denmark. *Acta Obstet Gynecol Scand* 1998;77:198-200.