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**Brief communication (Original)**

# Does GnRH agonist enhance the final adult height in girls with precocious puberty?

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***Background:*** Girls with sign of secondary sexual characteristic before the age of 8 years are defined as precocious puberty (PP). Early activation of hypothalamo-pituitary-gonadal axis causes central PP. Without treatment, some become short adult height and early menstruation may develop.

***Objective:*** Report the final adult height in precocious puberty girls who have been treated with GnRH agonist.

***Methods:*** Seventy girls with PP and early puberty (EP) who were treated with GnRH agonist have been followed up until they reach final height (FH). FH was compared with predicted adult height (PAH) before treatment and mid-parental height (MPH).

***Results:*** All subjects were treated with GnRH agonist for a mean duration of 1.9 0.6 years. FH was significantly higher than PAH before treatment (156.6±5.1 *vs*. 151.6±6 cm, $p < 0.001$). FH is positively correlated with MPH. However, treatment with GnRH agonist in EP girls and in PP girls with bone age of more than 12.5 years or those who already had menstruation may have less benefit.

***Conclusion:*** GnRH agonist can enhance FH in girls with PP. Early treatment in those with bone age of less than 12.5 years or before menstruation may result in good outcome.

***Keywords:*** GnRH agonist, early puberty, final adult height, precocious puberty

Precocious puberty (PP) is defined in girls as signs of puberty before the age of 8 years. Without treatment, some become short in adult height, compared to their mid-parental heights. Gonadotrophin-releasing hormone (GnRH) agonist delays bone age advancement and prevents early fusion of long-bone epiphyses, which eventually allows reaching target height. However, treatment of normal early puberty (EP) girls, whose breast development occurs between 8 to 9 years, or "advanced puberty" to manipulate growth and improve final adult heights, is still controversial. Girls with "advanced puberty" are at risk of short final adult height, especially those who have relatively short parents. Aim of this study is to report the outcome of treatment with GnRH analog in terms of final adult height in girls with precocious and early puberty.

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## Material and method

Seventy girls with precocious puberty (PP) and early puberty (EP), who were treated with GnRH agonist to improve their final height, had been followed up until they reach their final height. Central precocious puberty is defined as girls who have breast development before the age of 8 years and who have bone age advancement of more than 1 SD. Central precocious puberty was confirmed if the rising of LH after LHRH stimulation test or after the first dose of GnRH analog was in the pubertal range. No subjects had clinical symptoms or signs of CNS pathology, and some had MRI brain scans performed, which showed no abnormalities. Early puberty girls were defined as having breast development between 8 to 9 years of age where other pathological conditions were excluded. Bone age was performed in all cases and predicted adult height was estimated by the method of Bayley-Pinneau [1]. Mid-parental height was determined by (father's height + mother's height – 13)/2 [2]. GnRH agonist (Enantone L.P., Leuprolide, Takeda Pharmaceutical, Japan) 3.75 mg intramuscular

every four weeks was administered to delay bone age advancement and improve final height. Subjects were followed until they reached their final adult height (FH). Final adult height was defined when bone age was more than or equal to 14 years or height velocity was less than 1 cm/yr. FH was compared to PAH before treatment and MPH. Height gain was the difference between final adult height and PAH before treatment. SPSS version 11 was used in data analysis. Data was presented as mean and standard deviation. This study has been approved by the Ethic Committee, Faculty of Medicine, Chulalongkorn University.

## Results

At presentation, seventy PP and EP girls had a mean chronological age (CA) of 9.0  1.2 years and bone age (BA) of 11.4±1.4 year. All had a history of breast development at a mean age of 7.6±0.9 years. At presentation, 29 subjects (41%) had menarche at a mean age of 9.5±0.9 years. PAH at treatment started was significantly lower than MPH (151.6±6.7 *vs*. 155.5±3.8 cm, $p = 0.003$). During a mean duration of treatment with GnRH agonist for 1.9±0.6 years, height velocity (HV) was 4.6±1.4 cm/year at the first year and 4.1±1.4 cm/years at the second years. Weight gain was 5.0±2.3 kg and 3.7±2.8 kg at the first and second year of treatment, respectively. At the end of treatment, subjects had a mean CA of 11.0±0.7 year and BA of 12.4±0.9 years. PAH at treatment stopped was 156.5±5.5 cm, which was not different from MPH. After discontinuation of treatment, menstruation occurred at CA of 12.2±0.8 years. Subjects had been followed until they reached their FH at a mean age of 14.5±1.3 years and BA of 14.8±0.4 years. They gained height of 4.2±2.8 cm after menstruation. FH was significantly higher than PAH before treatment (156.6±5.1 *vs.* 151.6±6.7 cm, $p < 0.001$). Total height gain since treatment started, until subjects reached their final height, was 17.9±6.5 cm. In girls with bone age of less than 12.5 years at presentation, FH was also significantly different from PAH before treatment (156.6±5.1 *vs.*151.6±6.6 cm, $p < 0.001$) but this was not found in girls with BA more than 12.5 years at presentation. FH had a positive correlation with MPH ($r = 0.415$, $p = 0.01$). Those who had already had menstruation at presentation, reached their final height at 157.3±4.1 compared with PAH before treatment of 154.7±5.6 cm. Height gain was higher in girls who had no menstruation at presentation (FH 156.2±5.6 cm *vs.* PAH 151.1±6.8 cm).

Fifty-six girls of the PP group had a mean CA at presentation of 8.7±1.2 years and BA of 11.2±1.4 years. Twenty girls (35%) already had menarche at a mean age of 9.2±0.7 years. They were treated with GnRH analog for a mean period of 2.1±0.6 years. We found that FH was significantly different from PAH before treatment (156.4±4.9 *vs.* 151.2±6.6 cm, $p < 0.001$) but not different from MPH (156.4±4.9 *vs.* 155.6±3.7 cm). Fourteen girls with EP were treated with GnRH agonist at a mean age of 10.1±0.7 years for duration of 1.5±0.4 years. Treatment was discontinued at a mean age of 11.5±0.7 years and bone age of 12.9±0.7 years. Menstruation occurred at 12.5±0.8 years. These girls reached their FH at 157.4±5.7 cm compared with PAH before treatment of 153.2±7.5 cm.

In this study, FH had a positive correlation with MPH, height and weight at the start of treatment and height at end of treatment. Height gain had a positive correlation with HV at the first and second year of treatment.

**Table 1.** Clinical data of 70 girls, which consist of 56 girls with precocious puberty (PP) and 14 girls with early puberty (EP)

| | **Total (n = 70)** | **PP (n = 56)** | **EP (n = 14)** |
|---|---|---|---|
| Chronological age (yr) | 9.0±1.2 | 8.7±1.2 | 10.1±0.7 |
| Bone age (yr) | 11.4±1.4 | 11.2±1.4 | 12.1±0.8 |
| Menarche (%) | 29/70 (41%) | 20/56 (36%) | 8/14 (57%) |
| MPH (cm) | 155.5±3.8 | 155.7±3.6 | 154.7±4.6 |
| PAH at start (cm) | 151.6±6.7 | 151.2±6.6 | 153.2±7.5 |
| FH (cm) | 156.6±5.1 | 156.4±5.0 | 157.4±5.7 |
| Ht gain (cm) | 17.9±6.5 | 19.0±6.1 | 13.9±6.7 |
| Duration of treatment (yr) | 1.9±0.6 | 2.1±0.6 | 1.5±0.4 |

## Discussion

GnRH agonist has been widely used to improve final adult height in children with central precocious puberty (PP). Most of the reported data came from studies of girls because the prevalence of central precocious puberty is about 10 to 20 times higher in girls than in boys [3-5]. Reports from untreated patients show the mean loss of height compared to normal is about 10 cm in girls and 20 cm in boys [6, 7]. Carel *et al* reported that the final adult height increase is 4.8±5.8 cm over predicted adult height before treatment, and nearly half had height improvement of more than 5 cm [8]. However, other studies show various results ranged from 2.9 to 9.8 cm [ 9, 10]. Similarly, we demonstrate in this study that the improvement in height is about 5 cm over pretreatment predicted height, and final height is within the target height. A collaborative study of Lawson Wilkins and the European Society for Pediatric Endocrinology concluded that GnRH agonist does not significantly improve final adult height in girls with central PP whose age at diagnosis is greater than six years [11]. In addition, previous studies suggest that using the Bayley-Pinneau method for height prediction in untreated precocious puberty girls, is sometimes overestimated [6, 7, 10]. Their final height may be shorter than the estimated final adult height if they remain untreated. The cost of treatment for every 1 cm increase in height is 35,000 Thai Baht (approximately 1,100 USD) for medications alone. This is based on the price of GnRH agonist of 7,000 Thai Baht per vial in a public hospital and much more in the private sector.

The result of GnRH agonist to improve final height in girls with pubertal onset between 8 to 10 years is disappointing. Previous studies showed minor positive results in height improvement [13, 14]. In this study, final height is higher than PAH before treatment but does not reach statistical significance. However, we cannot draw a conclusion in this condition because of limited number of treated cases and lack of a control group. Bouvattier C *et* al reported lack of effect of GnRH agonist on final adult height in girls with advanced puberty. They demonstrated that the treated group had an average final height 3.4 cm over PAH before treatment but the positive effect on final height is only 1.4 cm compared with final height in the untreated or control group [15]. In addition, duration of treatment in this group was shorter than PP group. The amplitude of pubertal growth spurt varies negatively with age at puberty onset, representing a compensatory mechanism. However, this compensatory mechanism may not be complete and those who enter puberty at an early age may become shorter than those who enter later [16, 17]. Mean puberty height gain in all girls in our study was 17.9 cm, which is about 11.4% of the adult height. This can compare with puberty height gain of normal Thai girls in a previous study, which showed a pubertal height gain of 18.3 cm or 11.6% of normal adult height in Thai girls [18]. Total pubertal height gain in Thai girls is shorter than in other reports, which was about 15 to 20% of adult height. This may be due to low amplitude of growth spurt in Thai girls.

Genetic height potential is still an influence on the final height outcome in PP girls treated with GnRH agonist. In this study, girls with bone age of more than 12.5 years may not have benefits from GnRH agonist. Therefore, delay of treatment causes bone age advancement and this, eventually, results in the poor final height outcomes. Arrigo *et al* suggested that treatment with GnRH agonist in PP girls should be discontinued at a bone age of 12 to 12.5 years [19]. In addition, girls with menarche at presentation may gain less benefit than those without menarche. Therefore, parents should seek the medical advice at the earliest stage of puberty changes.

In conclusion, precocious puberty girls gain benefit from treatment with GnRH analog in terms of final adult height. Less benefit was demonstrated in early puberty girls. In PP girls, early treatment before menstruation or at bone age of less than 12.5 years results in a good outcome, especially this is true in those with tall parents.

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