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The Influence of GnRH Analog Therapy on Growth in Central Precocious Puberty

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Children with central precocious puberty (CPP) present various somatic and psychological abnormalities.
Objectives. The aim of the study was to evaluate growth changes in girls with central precocious puberty treated with GnRH analog therapy and to analyze the factors affecting the auxological response to this treatment.
Material and Methods. The study group consisted of 40 girls with puberty onset aged 6.0 ± 1.9 years (mean, ± SD), treated with 3.75 mg decapeptyl depot intramuscularly every 28 days. The treatment was initiated at the age of 7.5 ± 2.2 years and continued for 3.3 ± 2.3 years, until the age of 11.4 ± 0.9 years. Height (Ht), height standard deviation score (HtSDS), statural age, bone age and Ht prediction.
Results. During the treatment a decline in HtSDS from 2.0 ± 1.36 to 1.24 ± 1.0 was observed ($p = 0.0002$); and a deceleration in the maturation of bones of 1.0 ± 0.29 year in the first year and 0.66 ± 0.33 year in the following years ($p = 0.0008$). The HtSDS at the end of the treatment was significantly higher than was predicted in pretreatment (1.33 ± 1.04 vs. 0.07 ± 1.39, $p = 0.0005$). Ht and HtSDS after treatment were positively correlated with the predicted Ht (PAH) before treatment and negatively correlated with the bone age/statural age ratio before treatment ($p < 0.05$). The PAH before and after treatment correlated inversely with the bone age/statural age ratio ($p < 0.05$). Two subgroups were analyzed according to the patients' age when therapy was introduced: group 1 included girls who were under the age of 7 when therapy was introduced, and group 2 included girls aged 7 or older. There was a statistically significant difference in the PAH SDS before treatment between these two subgroups: Group I (–) 1.3 ± 1.8 vs. Group II (–) 0.14 ± 1.2 and there was no difference in the PAH SDS after treatment: Group I (–) 0.7 ± 1.1 vs. Group II 0.31 ± 1.2.
Conclusions. The child's age at the beginning of GnRHa therapy was an important predictor of height prognosis; the therapy introduced under the age of 7 improves the PAH during treatment. Height prediction during the entire treatment period is worse in children with more advanced bone age for their statural age at the onset of treatment (**Adv Clin Exp Med 2016, 25, 1, 27–32**).

Key words: growth, central precocious puberty, GnRH analog therapy.

Children with central precocious puberty (CPP) present various somatic and psychological abnormalities. CPP is associated with accelerated growth rate and bone maturation owing to precocious exposure to sex steroids leading to impairment of adult height (AH) [1, 2].

Therapy with gonadotropin-releasing hormone analog (GnRHa) is the treatment of choice in CPP. It has been proved to maintain the genetic height potential in children with CPP. Numerous research studies concerning the auxological results of GnRHa therapy in CPP have concentrated on the subjects' adult height [3–7].

This study was done to evaluate growth in girls with CPP who were treated with GnRHa. The aim of the study was to analyze the factors affecting the auxological outcomes of this therapy.

Material and Methods

The Patients

The study was carried out on 40 girls with CPP in whom puberty started at the age 6.0 ± 1.9 years (mean, ± SD). All the patients had idiopatic CPP. The diagnosis of idiopathic CPP was based on:

1. The onset of thelarche and/or menses at a chronological age (CA) less than 8 years;
2. An accelerated growth rate;
3. Bone age (BA) more than one year over the CA, with a ΔBA/ΔCA ratio more than 1.2;
4. A pubertal response to GnRH stimulation, with a plasma LH peak greater than 10 IU/L and a stimulated LH/stimulated FSH ratio more than 1.0 [8];
5. Pubertal uterine size and ovarian development (revealed by pelvic ultrasonography) [9];
6. No evidence of hypothalamo-pituitary abnormalities in magnetic resonance imaging.

Primary adrenal or gonadal diseases and other conditions that might influence puberty and growth were excluded.

The characteristics of the patients treated with GnRHa are shown in Table 1.

The Treatment

All the girls were treated with the depot form of the GnRH analog triptorelin (decapeptyl depot), Ferring Pharmaceuticals, Suffern, NY, USA), administered at a dose of 3.75 mg intramuscularly every 28 days.

After the CPP diagnosis, GnRHa treatment was initiated at the age of 7.5 ± 2.2 years, and was continued for 3.3 ± 2.3 years, until the age of 11.4 ± 0.9 years. Puberty suppression was confirmed by a GnRH stimulation test three months after the introduction of GnRHa treatment, and by evaluating basal LH, FSH and estradiol (E2) levels every six months during therapy. In all the patients the LH, FSH and E2 values were suppressed for the entire GnRHa treatment period.

The study design was accepted by the Ethics Committee of Wroclaw Medical University. A written informed consent was obtained from the parents of all the patients.

Methods

Height (Ht), height standard deviation score (HtSDS) and statural age, Ht prediction, body weight and bone age were evaluated before, during and after GnRHa therapy. Body height was measured every 28 days with a Harpender stadiometer [Holtain Ltd., Wales, United Kindom]. HtSDS and statural age were calculated according to Polish growth standards. Ht predictions were calculated by the Bayley-Pinneau method. Weight was measured with an electronic scale every 28 days. The pubertal stage was evaluated in accordance with Marshall and Tanner [10]. Bone age was determined according to the Greulich and Pyle method every 12 months [11].

Serum LH and FSH were measured by lumino-immunoassay (Byk-Sangtec Diagnostica GmbH, Dietzenbach, Germany). Serum estradiol was measured by microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). Uterine and ovarian volume and structure were evaluated by pelvic transabdominal ultrasonography using a 5-mHz Sonoline Prima device (Siemens Medical System, Inc. Ultrasound Group, Issaquah, WA, USA).

Statistics

The statistical analysis was done using STATISTCA 9 software (Statsoft Inc., Tulsa, OK, USA). Nonparametric tests were used: the Kolmogorov-Smirnov test, the Mann-Whitney *U* test and Spearman's rank correlation coefficient. A p-value less than 0.05 was considered statistically significant.

Table 1. The characteristics (mean ± SD) of 40 patients with CPP before and after GnRHa therapy. The onset of puberty was at age 6.0 ± 1.9 years; the treatment period was 3.3 ± 2.3 years

	Before treatment	At the end of therapy	P
CA (years)	7.5 ± 2.2	11.4 ± 0.9	
BA (years)	9.56 ± 2.14	12.4 ± 0.68	
BMI SDS CA	1.1 ± 0.9	1.0 ± 0.9	ns.
Overweight prevalence (%)	9.8	18.6	ns.
Obesity prevalence (%)	22.0	14.0	ns.
HtSDS CA	2.0 ± 1.36	1.24 ± 1.0	0.0002

CA – chronological age; BA – bone age; BMI SDS CA – body mass index standard deviation score for chronological age; HtSDS CA – height standard deviation score for chronological age.

Results

Table I presents the characteristics of the patients on initiation and after discontinuation of the treatment.

A prompt regression or arrest of the clinical symptoms of puberty was observed during the entire treatment period (3.3 ± 2.3 years).

Bone age (BA) before treatment was 9.56 ± 2.14 years. After the GnRHa therapy was completed, BA was 12.4 ± 0.68 years.

During the treatment period a decline in HtSDS from 2.0 ± 1.36 to 1.24 ± 1.0 was observed ($p = 0.0002$) (Fig. 1). BA decelerated 1.0 ± 0.29 year during the first year and 0.66 ± 0.33 year in the following years ($p = 0.0008$) (Fig. 2). The mean HtSDS was significantly higher at the end of the treatment than the mean pretreatment predicted height (PAH) SDS (1.33 ± 1.04 vs. –0.07 ± 1.39, $p = 0.0005$). The mean HtSDS was also significantly higher at the end of the treatment than the mean HtSDS at the time of last visit after the end of the treatment (1.23 ± 1.24, $p = 0.00005$) (Fig. 3). Ht and HtSDS were positively correlated after treatment with the predicted Ht (PAH) before treatment (Fig. 4), and negatively correlated with the bone age/statural age ratio before treatment ($p < 0.05$) (Fig. 5). Before and after treatment PAH correlated inversely with the bone age/statural age ratio ($p < 0.05$) (Fig. 6, 7).

Two subgroups were analyzed, according to the patients' age when GnRHa therapy was introduced. Group 1 consisted of girls under the age of 7 at the start of the therapy, and Group 2 included girls aged 7 and older. There was a statistically significant difference in the PAH SDS before treatment between these two subgroups: Group 1: (–) 1.3 ± 1.8 vs. Group 2: (–) 0.14 ± 1.2 ($p < 0.05$) and no significant difference in their PAH SDS after treatment: Group 1: (–) 0.7 ± 1.1 vs. Group 2: 0.31 ± 1.2. Thus, earlier introduction of GnRHa therapy, under the age of 7, results in a betterheight prognosis in girls with precocious puberty.

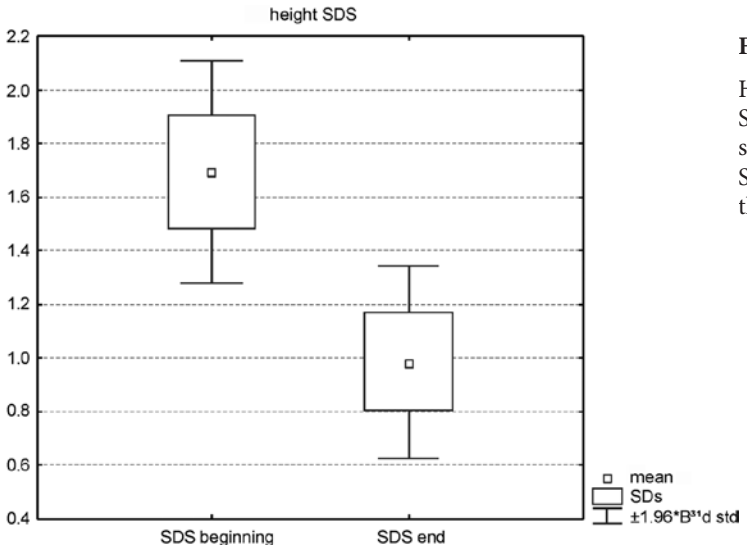

Fig. 1. Decline in height SDS ($p = 0.0002$)

Height SDS – height standard deviation score; SDS beginning – height standard deviation score at the beginning of GnRHa therapy; SDS end – height standard deviation score at the end of GnRHa therapy

Fig. 2. Deceleration of bone age (BA) in the first two years of GnRH treatment ($p = 0.0008$)

BA diff. in the first year – deceleration of bone age in the first year of GnRHa treatment; BA diff. in second year – deceleration of bone age in the second year of GnRHa treatment

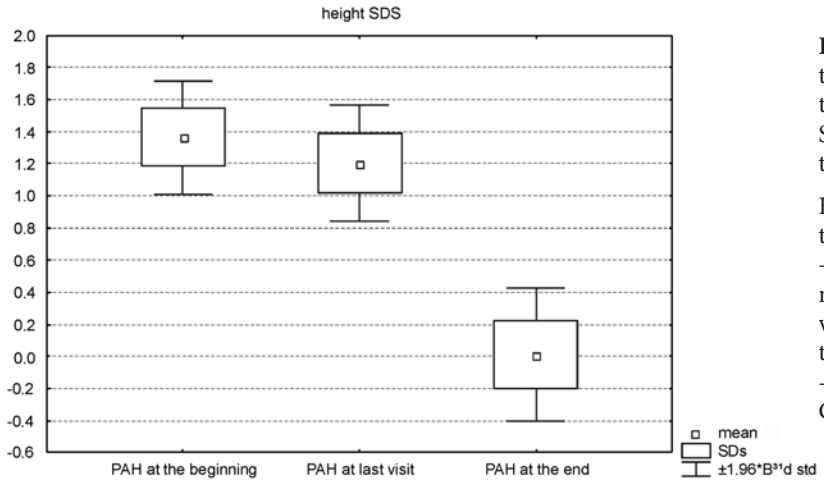

Fig. 3. Mean HtSDS at the end of treatment compared with mean pretreatment predicted height (PAH) SDS and mean HtSDS at the time of the last visit after treatment

Height SDS – height standard deviation score PAH at the beginning – predicted adult height at the beginning of GnRHa therapy; PAH at last visit – predicted adult height at the time of last visit; PAH at the end – – predicted adult height at the end of GnRHa therapy

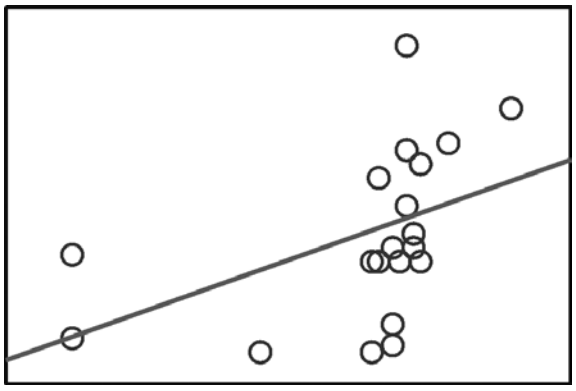

Fig. 4. Correlation between height SDS after treatment and predicted height (PAH) before treatment ($r = 0.69$, $p < 0.05$)

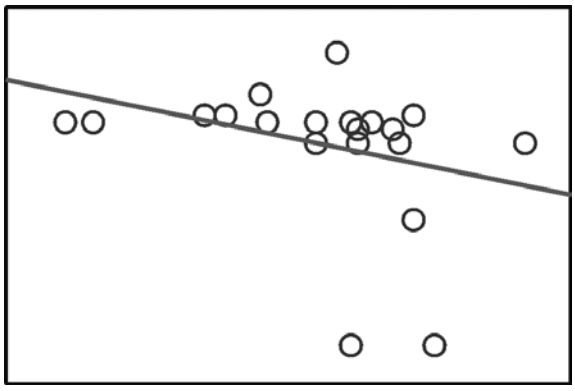

Fig. 6. Correlation between PAH SDS before treatment and bone age/statural age ratio after treatment ($r = -0.57$, $p < 0.05$)

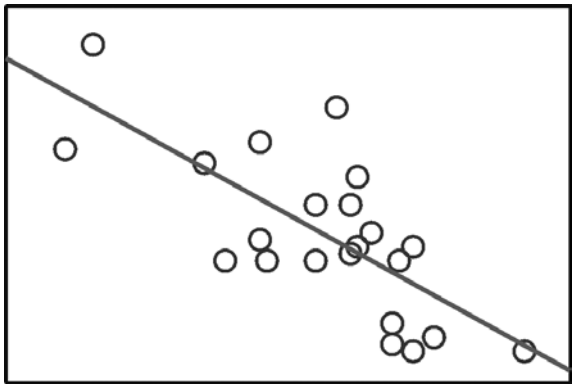

Fig. 5. Correlation between height SDS after treatment and bone age/statural age ratio before treatment ($r = -0.07$, $p < 0.05$)

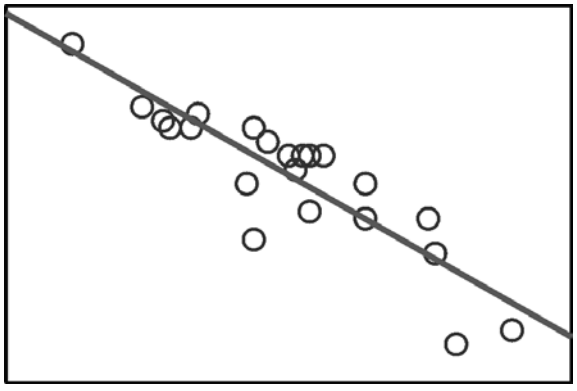

Fig. 7. Correlation between PAH SDS after treatment and bone age/statural age ratio after treatment ($r = -0.83$, $p < 0.05$)

Discussion

GnRHa therapy has been applied as the treatment of choice in CPP for about 30 years. The main aim of GnRHa therapy is to preserve the patient's height potential and to prevent psychosocial complications. The results of long-term studies concerning final auxological outcomes of this therapy have been the subject of numerous studies [3–5, 12–14]. The European Society for Pediatric Endocrinology (ESPE) has worked out a consensus concerning GnRHa therapy in children with CPP [15].

Factors influencing the final height outcomes in patients with CPP treated with GnRHa have

been analyzed. The greatest height gain (defined as adult height minus predicted adult height at baseline) was noted in girls with puberty onset under the age of 6 (mean height gain 9–10 cm) [12]. Decisions concerning GnRHa therapy in girls with puberty onset at an older age should be individualized.

Some studies have shown that GNRHa therapy was effective in improving final height only in girls with CPP onset under the age of 6 [5, 15]. Lazar et al. concluded that height gain after treatment was higher in CPP girls who were treated being under the age of 6 [5]. The results of the present study are consistent with these observations: The CPP girls who started GnRH therapy under the age of 7 had a better height prognosis after GnRHa treatment. Chiavaroli et al. analyzed the effect of GnRHa therapy on adult height in girls with early puberty (onset between the ages of 8 to 10) and found that the treatment had no positive impact on the girls' final height. Additionally, they noted that girls with early puberty have an increased risk of polycystic ovarian syndrome [16].

Moreover, a shorter interval between the onset of CPP and the initiation of GnRHa therapy has been shown to be an important factor in improving the effect of the therapy on final adult height [15, 17].

The initial prediction of adult height according to the Bayley-Pinneau method based on bone age enables CPP children with reduced growth potential who are at risk of short stature to be identified. These children benefit most from GnRHa therapy [18].

GnRHa treatment results in suppression of gonadotropin secretion, delaying the bone maturation and the growth rate, with an improvement in PAH. Children with more advanced bone age may present greater deceleration of osseous maturation and growth velocity [6, 13].

Lee et al. [12] investigated factors influencing adult height in girls with CPP who were treated with GnRHa. They proved that the growth rate during treatment was positively correlated with the patient's final height. The growth rate of their CPP patients was comparable to that of healthy prepubertal children at the same age (5–6 cm/year) during the first 72 weeks of therapy, and 4–4.5 cm/ /year from 72nd to the 192nd week of treatment. Girls with more advanced bone age (BA) over chronological age (CA) had a higher height gain over PAH during treatment. Because girls with more advanced BA have a lower PAH before GnRH therapy, slowing down bone maturation during treatment results in a better height gain than initially predicted. This, however, does not explains explain why these patients do not achieve their full potential adult height. Maintaining a growth rate comparable to that of prepubertal children leads to a better adult height outcome [12].

The growth velocity in some CPP patients decreases below the normal limit during GnRHa therapy. Weise et al. analyzed the influence of GnRHa treatment on the growth of 100 girls with CPP. They concluded that the impairment of growth resulted from the premature growth plate senescence under the influence of estrogens. BA is a marker for growth plate senescence. Growth velocity during GnRHa therapy was negatively correlated with BA advancement, the duration and stage of puberty and with serum estradiol concentration before treatment [19]. Similarly, in the current study Ht and HtSDS were negatively correlated after treatment with the difference between BA and statural age before treatment. The height prediction both before and after treatment was worse in girls with more advanced bone age.

According to Lee et al., subnormal growth velocity during GnRHa therapy may be associated with a decrease in growth hormone and IGF-1 secretion due to suppression of gonadal steroids. The addition of growth hormone to GnRH therapy may improve the adult height in these patients [20, 21].

Several studies have shown a relationship between GnRHa treatment duration and adult height. The optimal height prognosis was observed when GnRHa therapy was discontinued at a chronological age (CA) of about 11 years and bone age (BA) of about 12 years. However, the decision to end GnRHa therapy should be based on an analysis of all the variables, including CA, BA, the duration of the therapy, growth velocity and target height [12, 15, 22].

The study has shown that GnRHa treatment has beneficial effect on height potential in most patients, especially in younger ones and those with a rapid progression of CPP. The authors plan a follow-up study of this group of patients after GnRHa treatment in order to evaluate the long-term impact of the therapy on their final height and the course of puberty.

The authors concluded that the patient's age at the beginning of GnRHa therapy is an important predictor of height prognosis. Beginning therapy under the age of 7 improves the predicted adult height (PAH) during treatment. Height prediction during the entire treatment period is worse in children with a more advanced bone age compared with their statural age at the onset of treatment.

References

[1] **Partsch JC, Heger S, Sippell WG:** Management and outcome of central precocious puberty. Clin Endocrinol 2002, 56, 129–148.

[2] **Chemaitilly W, Trivin C, Adan L, Gall V, Sainte-Rose C, Brauner R:** Central precocious puberty: clinical and laboratory features. Clin Endocrinol 2001, 54, 289–294.

[3] **Heger S, Partsch CJ, Sippell WG:** Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. J Clin Endocrinol Metab 1999, 84, 4583–4590.

[4] **Paterson WF, McNeill E, Young D, Donaldson MD:** Auxological outcome and time to menarche following long-acting goserelin therapy in girls with central precocious or early puberty. Clin Endocrinol 2004, 61, 626–634.

[5] **Lazar, Padoa A, Phillip M:** Growth pattern and final height after cessation of gonadotropin-suppressive therapy in girls with central sexual precocity. J Clin Endocrinol Metab 2007, 92, 3483–3489.

[6] **Fuqua JS:** Treatment and outcomes of precocious puberty: An update. J Clin Endocrinol Metab 2013, 98, 2198–207.

[7] **Mul D and Hughes IA:** The use of GnRH agonists in precocious puberty. Eur J Endocrinol 2008, 159, S3–S8.

[8] **Pescovitz OH, Hench KD, Barnes KM, Loriaux DL, Cutler GB Jr:** Premature thelarche and central precocious puberty: the relationship between clinical presentation and the gonadotropin response to luteinizing hormone-releasing hormone. J Clin Endocrinol Metab 1988, 67, 474–479.

[9] **Briges NA, Cooke A, Healy MJ, Hindmarsh P, Brook CGD:** Standards for ovarian volumes in childhood and puberty. Fertil Steril 1993, 60, 456–460.

[10] **Marshall WA, Tanner JM:** Variations in the pattern of pubertal changes in girls. Arch Dis Child 1969, 44, 291–303.

[11] **Greulich WW, Pyle SI:** Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford, CA: Stanford University Press 1959.

[12] **Lee PA, Neely EK, Fuqua J, Yang D, Larsen LM, Mattia-Goldberg C, Chwalisz K:** Efficacy of leuprolide acetate 1-month depot for central precocious puberty (CPP): growth outcomes during a prospective, longitudinal study. Int. J Pediatr Endocrinol 2011, 2011–2017.

[13] **Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R:** Long-Term Observation of 87 Girls with Idiopathic Central Precocious Puberty Treated with Gonadotropin-Releasing Hormone Analogs: Impact on Adult Height, Body Mass Index, Bone Mineral Content, and Reproductive Function. J Clin Endocrinol Metab 2008, 93, 190–195.

[14] **Neely EK, Lee PA, Bloch CA, Larsen L, Di Yang, Mattia-Goldberg C, Chwalisz K:** Leuprolide Acetate 1-Month Depot for Central Precocious Puberty: Hormonal Suppression and Recovery. Int J Pediatr Endocrinol 2010, Article ID 398639, 9 pages. DOI:10.1155/2010/398639.

[15] **Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR: ESPE-LWPES GnRH Analogs Consensus Conference Group, Antoniazzi F, Berenbaum S, Bourguignon J, Chrousos GP, Coste J, Deal S, de Vries L, Foster C, Heger S, Holland J, Jahnukainen K, Juul A, Kaplowitz P, Lahlou N, Lee MM, Lee P, Merke DP, Neely EK, Oostdijk W, Phillip M, Rosenfield RL, Shulman D, Styne D, Tauber M & Wit JM:** Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009, 123, 752–762.

[16] **Chiavaroli V, Liberati M, D'Antonio F, Masuccio F, Capanna R, Verrotti A, Chiarelli F, Mohn A:** GNRH analog therapy in girls with early puberty is associated with the achievement of predicted final height but also with increased risk of polycystic ovary syndrome. Eur J Endocrinol 2010, 163, 55–62.

[17] **Brito VN, Latronico AC, Cukier P, Teles MG, Silveira LF, Arnhold IJ, Mendonca BB:** Factors determining normal adult height in girls with gonadotropin-dependent precocious puberty treated with depot gonadotropin-releasing hormone analogs. J Clin Endocrinol Metab 2008, 93, 2662–2669.

[18] **Bar A, Linder B, Sobel EH, Saenger P, DiMartino-Nardi J:** Bayley-Pinneau method of height prediction in girls with central precocious puberty: correlation with adult height. J Pediatr 1995, 126, 955–958.

[19] **Weise M, Flor A, Barnes KM, Cutler GB, Baron J:** Determinants of growth during gonadotropin-releasing hormone analog therapy for precocious puberty. J Clin Endocrin Metab 2004, 89, 103–107.

[20] **Lee PA:** The Effects of Manipulation of Puberty on Growth Horm Res 2003, 60, Suppl 1, 60–67.

[21] **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, 1005–1010.

[22] **Arrigo T, Cisternino M, Galluzzi F:** Analysis of the factors affecting auxological response to GnRH agonist treatment and final height outcome in girls with idiopathic central precocious puberty. Eur J Endocrinol 1999, 141, 140–144.

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