Research

Growth and Adult Height during Human Growth Hormone Treatment in Chinese Children with Multiple Pituitary Hormone Deficiency Caused by Pituitary Stalk Interruption Syndrome: A Single Centre Study

Short title: Growth and adult height of PSIS children

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Abstract

Background: The aim of this study was to assess growth velocity (GV) during hGH treatment of children with MPHD caused by PSIS and to analyze the characteristics of patients that attain normal adult heights.

Methods: Data from 74 (58 males/16 females) children with MPHD caused by PSIS with GH, TSH, gonadotropin and ACTH deficiencies were collected. Subjects were divided into groups containing 12 pre-pubescent females (Female-Group) and 36 pre-pubescent males (Male-Group 1). The remaining 24 males were further sub-divided into 2 groups (Male-Group2 and Male-Group3) according to the initiation of gonadotropin treatment.

Results: We observed no differences in ΔHtSDS and GV at different time points of hGH treatment between Female- and Male-Group 1 (P > 0.05). The GV in the first year was higher than the second year of hGH treatment (P = 0.011 for Female-Group, ≤ 0.001 for Male-Group 1, P = 0.005 for Male-Group 2, and P = 0.046 for Male-Group 3). Additionally, 23 (19 males and 4 females) patients reached adult height after treatment. The total gain in height positively correlated with the GV during the first year (R = 0.626, P ≤ 0.001).

Conclusion: GVs during hGH treatment were similar amongst pre-pubescent males and females with MPHD caused by PSIS. The GV during the first year of hGH treatment is therefore an effective predictor of future height outcomes in patients with MPHD caused by PSIS.

Key words: pituitary stalk interruption syndrome (PSIS), growth velocity (GV), human growth hormone (hGH) treatment, adult height.

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Background

Pituitary stalk interruption syndrome (PSIS) is characterized by the occurrence of a thin or absent pituitary stalk, hypoplasia of adenohypophysis, and ectopic neurohypophysis on magnetic resonance imaging (MRI) of the hypothalamo-pituitary (H-P) region (1). It is a rare congenital disease associated with multiple pituitary hormone deficiencies (MPHD). MPHD, by definition, represents an impaired production of one or more anterior pituitary hormones in addition to growth hormone (GH) and is a chronic, lifelong condition (2,3,4).

Children with PSIS typically present with growth reduction and delayed puberty, leading to significant distress to children and their families. Recombinant human growth hormone (hGH) treatment is the optimal therapy for short stature in children with isolated growth hormone deficiency (IGHD) and can effectively increase height velocity to attain adult heights within the target range (5,6). Whether the benefits of hGH treatment in patients with MPHD caused by PSIS are consistent with those observed in IGHD remains undefined.

In this study, we assessed the growth velocity (GV) of patients with MPHD caused by PSIS who were administered hGH. We further analyzed the characteristics of patients that subsequently attained adult heights.

Methods

Patients and grouping
In this retrospective study, data from patients diagnosed with PSIS during childhood and adolescence were collected in the pediatric endocrine outpatient facility of Shandong Provincial Hospital Affiliated to Shandong University, from January 2008 to November 2018. In total, 74 patients (58 males and 16 females) with confirmed GH, thyroid stimulating hormone (TSH), gonadotropin and adrenocorticotropic hormone (ACTH) deficiencies were analyzed. No patients had spontaneous puberty development and puberty was induced via gonadotropin or sex hormone treatment. Amongst these patients, 48 (36 males and 12 females) received hGH treatment and other deficient hormones excluding gonadotropin during the study period and were pre-pubescence. Subjects were divided into the Female-Group (n=12) and Male-Group 1 (n=36). Additionally, 13 patients (10 males and 3 females) were treated with hGH followed by gonadotropin which was administered with age. These 10 male patients formed the Male-Group 2. Lastly, 13 subjects (12 males and 1 female) received initial hGH and gonadotropin treatment. These 12 males were grouped into Male-Group 3.

**Ethics**
Ethics Committee Approval: The study was approved by the Medical Ethics Committee of Shandong Provincial Hospital affiliated to Shandong University (NO. 2019-053). Informed Consent: Patients or their parents/guardians provided verbal consent for their non-identifiable data to be collated and analyzed.

**Diagnostic criteria**
The diagnosis of PSIS was based on MRI scans of the hypothalamus and pituitary gland (an absent or thin pituitary stalk, hypoplasia of the anterior pituitary gland, and ectopic location of posterior pituitary), MRI scans were performed using a 3.0 T Scanner (Siemens, Erlangen, Germany) in the sagittal and coronal planes on T1 and T2 weighted imaging (3 mm thickness).

Bone age (BA) was determined by left hand and wrist X-ray images according to the methods of Greulich and Pyle. Hypophyseal hormone levels were examined in each patient. The pituitary axis was examined using the following tests: (1) Growth hormone deficiency (GHD) diagnosed in the absence of a significant peak in GH secretion after ≥ 1 stimulation test. Diagnosis was based on GH peak levels < 10 µg/ml following two independent GH provocation tests (i.e. IV arginine test, 0.5 mg/kg; maximum dosage: 30 mg; oral levodopa test: 10 mg/kg; maximum dosage: 500 mg). **Patients received GH provocation tests on the basis of normal thyroid and adrenal functions.** (2) TSH deficiency was defined as low serum free T4 (FT4 < 12.0 pmol/l) (reference range: 12.0-22.0 pmol/l) with concomitantly normal or decreased serum TSH (reference range: 0.27-4.2 uIU/ml). (3) ACTH deficiency was assessed by either decreased serum cortisol (COR) levels in the morning (COR < 138 nmol/l) or an impaired cortisol serum concentration increase (COR < 550 nmol/l) during insulin-induced hypoglycemia with inappropriately low serum ACTH concentrations. (4) Gonadotropin deficiency was based on the gonadotropin hormone-releasing hormone-stimulation test (triptorelin: 2.5 µg/kg administered as a subcutaneous injection at a maximum dosage of 100 µg with a cut-off point of a blunted response: 2.8 mIU/ml for luteinizing hormone (LH) and/or 3.7 mIU/ml for follicle-stimulating hormone (FSH)); or basal levels of FSH and LH below the sensitive range of the assay (0.1 mIU/ml) on the basis of delayed or absent pubertal development (7,8). Serum GH levels were measured using chemiluminescence assays (Cobas E170, Roche Diagnostics, Germany). Serum FT4, TSH, ACTH, COR, FSH and LH were measured using chemiluminescence assays (Siemens Healthcare Diagnostics, USA). All patients underwent the same testing protocol and all tests were performed after overnight fasting.

**Height and weight**
Height was measured in the morning by the same medical team and expressed in cm. Height measurements were standardized to age and sex and expressed as standard deviation scores (HtSDS) relative to chronological age (CA) according to Growth Charts for Chinese Children and Adolescents (2009). The GV during hGH treatment was analyzed each year and was calculated in cm through the difference in previously recorded height. ΔHtSDS was calculated by the difference from the previously recorded HtSDS.

Weight was measured in the morning, in the fasting state, and at each visit and expressed in kg. BMI was calculated as the weight (kg) divided by the height squared (meters). BMI values were transformed into BMISDS, based on Normative Values for Chinese Children and Adolescents (2009) to minimize the confounding effects of age and sex.

**Treatment and follow-up**
Patients received hormone replacement therapy according to pre-determined hormone abnormalities. Hydrocortisone and L-Thyroxin were immediately administered once ACTH and TSH deficiency were confirmed. The dosages of hydrocortisone were 10-15 mg·m^{-2}·d^{-1}, oral administration, divided into two daily doses. The dosages L-Thyroxin were 1.5-2.0 µg·kg^{-1}·d^{-1}, oral administration, qd. The dosages of hydrocortisone and L-Thyroxin were adjusted to maintain the levels of FT4, COR, blood glucose and serum electrolytes within normal range. HGH was administered on the basis of normal thyroid and adrenal functions, and patients were administered Hydrocortisone and L-Thyroxin from hormone deficiency diagnosis. HGH was produced by ChangChun GeneScience Pharmaceuticals Co., Ltd. The dosage of hGH was 0.10-0.15 IU·kg^{-1}·d^{-1}), daily injection, for 7 days/week. Puberty was initiated in 26 patients through the administration of gonadotropin.
(exogenous human chorionic gonadotropin (hCG) and/or urine-derived human menopause gonadotropin (hMG)) therapy. HCG and hMG were produced by Livzon Pharmaceutical Group Inc., China. The dosage of hCG was 2000 IU, twice a week, given intramuscularly for males, whilst hMG was 75 IU, twice a week, intramuscularly for females. Boys had a pretreatment phase of hCG for 3 months. As serum testosterone (TO) reached normal values, hCG combined with hMG were administered to improve sexual development. If the TO levels remained subnormal, exogenous TO (testosterone undecanoate: 80–160 mg·d⁻¹, oral administration) was administered to induce puberty (9).

All patients were followed in our outpatient facility at 3 months intervals. The compliance to treatment was assessed at each visit, and patients underwent complete physical examinations by the same medical team, including the collection of height and weight measurements during and after treatment. Laboratory chemistry and hormone profiles were also assessed.

Statistical analysis
Data were analyzed using IBM SPSS software (IBM SPSS for Windows, Version 25; IBM Corp., Armonk, NY, USA, 2017). Descriptive statistics of the quantitative variables are presented as means ± standard deviation (SD). Differences between groups of continuous data were compared using the independent-sample t test. Pearson's correlation was used to assess the relationships between various parameters. The threshold for statistical significance was 0.05.

Results
1. GV of pre-pubertal patients treated with hGH alone
CA, BA, BMI SDS and HtSDS during hGH treatment were 8.51 ± 3.08 years, 4.51 ± 2.75 years, -0.20 ± 1.11 and -3.60 ± 1.76 in the Female-Group and 8.94 ± 3.42 years, 5.51 ± 3.22 years, 0.20 ± 1.35 and -2.97 ± 1.23 in the Male-Group 1. There were no differences in CA and BA, BMI SDS and HtSDS at hGH treatments between pre-pubescent females (Female-Group) and males (Male-Group 1), \( P = 0.698, P = 0.653, P = 0.358 \) and \( P = 0.175 \). The CA was significantly larger than the BA in both groups \( (P = 0.006 \) for Female-Group and \( P \leq 0.001 \) for Male-Group 1) (Fig 1A).

For Female-Group patients, the HtSDS was -2.39 ± 1.60 and -1.98 ± 1.54 after 1 and 2 years hGH treatment, respectively. The HtSDS was -1.85 ± 1.14 and -1.47 ± 0.86 after 1 and 2 years of hGH treatment in Male-Group 1. There were no difference in HtSDS at any point during hGH treatment \( (P = 0.292 \text{ and } P = 0.157) \). For Female-Group patients, the GV was 11.63 ± 2.38 cm/y in the first year and 9.37 ± 1.48 cm/y in the second year. The GV of Male-Group 1 in the first year was 11.95 ± 2.62 cm/y compared to 9.83 ± 1.71 cm/y in the second year. No differences in GV at any timepoint during hGH treatment between pre-pubescent females (Female-Group) and males (Male-Group 1) \( (P = 0.710 \) for the first year and \( P = 0.410 \) for the second year) were observed. GV in the first year was higher than in the second year for both two groups \( (P = 0.011 \) for the Female-Group and \( P \leq 0.001 \) for the Male-Group 1) (Fig 1B). The \( \Delta \text{HtSDS1} \) for the Female- and Male-Group 1 were significantly higher than the \( \Delta \text{HtSDS2} \) values \( (1.21 \pm 0.51 \text{ vs } 0.59 \pm 0.38 \text{ and } P \leq 0.001 \) for Female-Group, \( 1.13 \pm 0.57 \text{ vs } 0.70 \pm 0.47 \text{ and } P = 0.003 \) for Male-Group 1, respectively) (Fig 1C).

Detailed information is shown in Table 1.

2. GV of patients with PSIS (Male-Group 2 and Male-Group 3) treated with hGH and gonadotropin
Detailed information of CA, BA, height SDS and GV during hGH or gonadotropin treatment are shown in Table 1-2. The CA following hGH treatment of the Male-Group 2 was larger than BA \( (11.24 \pm 2.99 \text{ vs } 6.55 \pm 3.82 \text{ years, } P < 0.009) \). No differences in CA and BA at the initiation of hGH treatment between Male-Group 1 and Male-Group 2 were observed \( (P = 0.660 \text{ and } P = 0.390) \), respectively. CA at the initiation of hGH treatment (hGH + gonadotropin treatment) of Male-Group 3 was larger than BA \( (17.42 \pm 3.32 \text{ vs } 12.25 \pm 1.37 \text{ years, } P \leq 0.001) \). The CA of Male-Group 3 was significantly higher than that of Male-Group 1 and Male-Group 2 \( (P \leq 0.001 \) which was also observed for BA values \( (P \leq 0.001) \).

The GV during the first two years of hGH treatment in the Male-Group 2 were 13.37 ± 2.45 and 10.08 ± 2.16 cm/year. GV during the first two years of hGH (hGH + gonadotropin) treatment of Male-Group 3 were 10.68 ± 3.59 and 8.16 ± 2.03 cm/year. We observed no differences in GV during the first year of hGH treatment amongst the three groups \( (P = 0.132 \) between Group 1 and Group 2, \( P = 0.193 \) between Group 1 and Group 3, and \( P = 0.058 \) between Group 2 and Group 3). During the second year, no differences in GV were observed between Groups 1 and 2 \( (P = 0.701) \), but the GV of Group 3 was significantly lower than the other two male groups \( (P = 0.007 \) between Male-Group 1 and Male-Group 3, and \( P = 0.044 \) between Male-Group 2 and Male-Group 3).

GV during the first year of hGH treatment was higher than the second year for the three groups \( (P \leq 0.001 \) for Male-Group 1, \( P = 0.005 \) for Male-Group 2 and \( P = 0.046 \) for Male-Group 3, respectively) (Fig 1B). The differences in \( \Delta \text{HtSDS} \) between the first and second year of hGH treatment for Male-Group 2 were also statistically significant \( (1.39 \pm 0.58 \text{ vs } 0.77 \pm 0.41, P = 0.013) \). However, differences in the \( \Delta \text{HtSDS} \) during the first two years of hGH treatment did not change in the Male-Group 3 \( (1.50 \pm 0.79 \text{ vs } 1.02 \pm 0.76, P = 0.144) \) (Fig 1C).
The CA during the initiation of hGH + gonadotropin treatment of Male-Group 2 (13.39 ± 2.80) were significantly lower than those of Male-Group 3 (P = 0.007), but no differences in BA at the initiation of hGH + gonadotropin treatment between the groups were observed (P = 0.866). The GV in the first year of hGH + gonadotropin treatment in Group 3 was significantly higher than that of Group 2 (P = 0.041), which was similar for ΔHtSDS (P = 0.004).

3. Characteristics of patients achieving adult height
In total, 23 patients (19 males and 4 females) with PSIS reached adult height following hGH treatment. For male patients, 18/19 attained normal adult height (height SDS > -2), yet only 7 reached a height above the 50th percentile (adult height ≥ 172.7 cm or adult HtSDS ≥ 0). For females, all patients (4/4) reached a normal adult height range and all were above the 50th percentile (adult height ≥ 160.6 cm or adult HtSDS > 0).

The mean adult height was 168.5 ± 6.1 cm (HtSDS = -0.47±1.11) for males and 164.0 ± 2.9 cm (HtSDS = -0.77±0.49) for females. The parental target height was 170.1 ± 4.9 cm (HtSDS = -0.43±0.82) for males and 160.8 ± 1.3 cm (HtSDS = 0.26±0.03) for females. The age at initiation of hGH treatment of females was 10.4 ± 0.8 years, and 14.4 ± 3.5 years for males. The BA at initiation of hGH treatment of females was 8.4 ± 0.8 years and 9.9 ± 3.5 years for males. HtSDS at hGH treatment onset was -3.11 ± 1.86 for males and -1.75 ± 0.23 for females, respectively. The GVs in the first year of hGH treatment were 11.0 ± 3.2 cm and 12.9 ± 1.9 cm for males and females, respectively. The total height gain was 23.9 ± 15.6 cm and 20.9 ± 4.9 cm for males and females, respectively.

A negative correlation between the total height gain and BA at hGH onset and height at hGH treatment onset (R ≤ -0.721, P ≤ 0.001; and R = -0.822, P ≤ 0.001, respectively) were observed. Moreover, a positive correlation was observed between total height gain and GV in the first year of hGH treatment (R = 0.826, P ≤ 0.001). Figure 2 graphically depicts these correlations.

Discussion
PSIS as the most common cause of MPHD, was first reported by Fujisawa et al. in 1987 (10). Various anterior pituitary hormone deficiencies and clinical presentations are common in PSIS patients. To date, studies on the growth of children and adolescents with PSIS during the course of hGH treatment are sparse and continuous follow-up to adult age is rarely reported (4). In this retrospective study, measurements were performed in 74 patients with PSIS. Our analysis included long-term patient follow-up performed at short intervals by the same team of healthcare professionals. Despite certain limitations, the results provided various noteworthy observations. We found that the addition of gonadotropin could affect the GV in pubertal children (4), so male PSIS patients were divided into three groups on the basis of their gonadotropin treatment protocols.

All children short in stature can receive hGH treatment to decrease linear height deficits. The CA of PSIS patients receiving hGH treatment were older than those of previous studies. Chinese parents are familiar with the idea of “delayed puberty”, leading to a higher referral age. A large number of children were from rural areas with an undeveloped economy, in which the attention to growth and development is low. These factors contribute to the late CA of PSIS children and adolescents. The BA of all the PSIS children in our study were lower than their CA as previously described (4). GH deficiency leads to slow bone growth and maturity, owing to delayed BA. The treatment effect at different time points was independent of the gender amongst pre-pubescent PSIS children in this study. This differed to previous studies (11) in which pre-pubescent boys had a greater response to hGH treatment than pre-pubescent girls with GHD who were small for their gestational age (SGA). Deficiencies in other pituitary hormones may weaken the responses of males, and the low number of patients may have contributed to the discrepancies. The BMI SDS of pre-pubescent boys were higher than those of females though the differences were not statistically significant. The increase in BMISDS may have adverse effects on height growth in shorter male children, consistent with that reported in previous studies (12).

In previous studies on congenital IGHD patients, the GV in the first year of hGH therapy was 8.92 ± 2.99 cm for males and 8.17 ± 3.15 cm for females (13). The GV in the first year of hGH treatment was significantly higher than that of GH deficient patients (P ≤ 0.001 for males and P = 0.004 for females), whilst the CA values were similar (P = 0.170 for males and P = 0.272 for females). The differential responses to hGH treatment may be due to the high sensitivity to hGH and/or severity of GH deficiency of the PSIS patients (14). The GV of patients in the Female-Group, Male-Group1, Male-Group-2 and Male-Group 3 in this study were higher in the first year compared to the second year, consistent with previous studies and confirming that GHD children show faster linear growth during the initial stages of GH therapy (15) in addition to other studies on congenital MPHD (4). Although the CA and BA of Male-Group 3 were higher than those of the other two male groups, the GV during the first two years of hGH treatment were similar, which may be explained by the induction of puberty. The induction of puberty leads to height spurts which may explain the response to hGH treatment observed.

In previous GHD studies, only one third of patients reached normal adult height in response to hGH treatment (13). The duration of hGH treatment, age at initiation of hGH treatment, and ethnicity may contribute to the discrepancies between this and previous studies. Although girls and boys had similar responses to hGH at
different time points pre-puberty, females reached a larger adult height than males in this study. The younger age at the initiation of hGH treatment of females and small sample size may explain this enhanced treatment effect. A positive correlation between total height gain and GV in the first year of hGH treatment was in accordance with previous studies (16). The total height gain in the first year of hGH is an effective predictor of future height outcomes (17,18,19,20). Previous studies on GHD also indicate the importance of early treatment with hGH for IGHD patients (21,22). The negative relationship of BA and total height gain in this study also reflects a similar phenomenon in patients with PSIS and the total height gain may be greater if patients receive hGH at an earlier stage. This can be explained by the fact that the early initiation of hGH permits a longer duration of treatment and larger gains in height.

**Study limitations**

The uneven number of male and female patients and differences in duration of hGH treatment may have influenced the results. Especially the number of female patients who attained adult height was only 4. It is not possible to reach a complete conclusion about characteristics of female patients and number of female patients is too low to compare with male patients in result. So this study was lack of the comparison between males and females on some data. And data regarding the sexual development of PSIS patients should also have been collected and analyzed. These limitations should be addressed in future studies.

**Conclusions**

Males and females with MPHD caused by PSIS had a similar GV during hGH treatment before puberty. The GV during the first year of hGH treatment can predict future height outcomes for patients with MPHD caused by PSIS. PSIS patients can attain normal adult heights following hGH treatment.

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**Authorship contributions**

Medical Practices: Fengxue Wang, Jinyan Han, Zengmin Wang, Xiaohong Shang

Concept: Guimei Li

Design: Fengxue Wang, Guimei Li

Data Collection or Processing: Fengxue Wang, Jinyan Han, Zengmin Wang, Xiaohong Shang

Analysis or Interpretation: Fengxue Wang, Jinyan Han, Guimei Li

Literature Search: Zengmin Wang, Xiaohong Shang

Writing: Fengxue Wang, Jinyan Han

**Conflict of Interest**

No conflict of interest.

**Financial Disclosure**

No financial disclosure.

**References**

metabolisme 2014;46:668-673.
Figure 1.

![Graph A](image1)

**Females**  
**Group 1**  
**Group 2**  
**Group 3**

Figure 2.

![Graph B](image2)

Table 1. Characteristics of the patients with PSIS treated with hGH

<table>
<thead>
<tr>
<th></th>
<th>Female-Group (N=12)</th>
<th>Male-Group1 (N=36)</th>
<th>Male-Group2 (N=10)</th>
<th>P*</th>
<th>P#</th>
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<tbody>
<tr>
<td>CA (years) at hGH onset</td>
<td>8.51 ± 3.08</td>
<td>8.94 ± 3.42</td>
<td>11.24 ± 2.99</td>
<td>0.060</td>
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<tr>
<td>BA (years) at hGH onset</td>
<td>4.91 ± 2.75</td>
<td>5.51 ± 3.22</td>
<td>6.55 ± 3.82</td>
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<tr>
<td>BMI SDS at hGH onset</td>
<td>-0.20 ± 1.11</td>
<td>0.20 ± 1.35</td>
<td>-0.02 ± 1.66</td>
<td>0.667</td>
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<tr>
<td>HtSDS 1st year of hGH treatment onset</td>
<td>-3.60 ± 1.76</td>
<td>-2.97 ± 1.23</td>
<td>-3.43 ± 2.67</td>
<td>0.435</td>
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<td>-2.39 ± 1.60</td>
<td>-1.85 ± 1.14</td>
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<td>-1.98 ± 1.54</td>
<td>-1.47 ± 0.86</td>
<td>-1.69 ± 1.92</td>
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<tr>
<td>HtSDS 2nd year of hGH treatment</td>
<td>-0.668</td>
<td>1.21 ± 0.51</td>
<td>1.13 ± 0.57</td>
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<td></td>
<td>0.467</td>
<td>0.59 ± 0.38</td>
<td>0.70 ± 0.47</td>
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<tr>
<td>GV (cm/year)</td>
<td>1.39 ± 0.58</td>
<td>0.77 ± 0.41</td>
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<tr>
<td></td>
<td>Male-Group2 (N=10)</td>
<td>Male-Group3 (N=12)</td>
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<tr>
<td>CA (years) at hGH+ gonadotropin onset</td>
<td>13.39 ± 2.80</td>
<td>17.42 ± 3.32</td>
<td>0.007</td>
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<tr>
<td>BA (years) at hGH+ gonadotropin onset</td>
<td>10.85 ± 2.00</td>
<td>12.25 ± 1.37</td>
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<tr>
<td>BMI SDS at hGH+ gonadotropin onset</td>
<td>0.43 ± 1.53</td>
<td>0.33 ± 0.94</td>
<td>0.853</td>
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</table>

**Height SDS**

- 1st year of hGH+ gonadotropin treatment: -0.84 ± 1.96 vs. -3.60 ± 1.74, *P* = 0.002
- 2nd year of hGH+ gonadotropin treatment: -0.02 ± 1.14 vs. -2.09 ± 1.21, ≤0.001

**ΔHt SDS**

- ΔHt SDS1 hGH+ gonadotropin treatment: 0.49 ± 0.62 vs. 1.50 ± 0.79, *P* = 0.004
- ΔHt SDS2 hGH+ gonadotropin treatment: 0.40 ± 0.75 vs. 1.02 ± 0.76, 0.070

**Growth velocity (cm/year)**

- 1st year of hGH+ gonadotropin treatment: 7.93 ± 1.87 vs. 10.68 ± 3.59, *P* = 0.041
- 2nd year of hGH+ gonadotropin treatment: 8.10 ± 2.16 vs. 8.16 ± 2.03, 0.947