Delaying puberty with GnRHa does not promote adult height in GH treated children who enters puberty at average age.

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Introduction

Treatment with recombinant human GH (rhGH) promotes adult height (Ht) but with large individual differences in response[1]. Early rhGH start improves outcome. Combining rhGH with a Gonadotroping Releasing Hormone-analog (GnRHa) to delay puberty may be useful. Treatment with rhGH+GnRHa results in greater adult height compared to rhGH monotherapy in children with pubertal start in the early normal age range[2,3] or is not better than rhGH monotherapy[4]. This study assess if rhGH or rhGH + GnRHa is more effective in improving adult height in short children starting puberty close to average and also compare to non-treated controls.

Objectives

- To examine adult height in children with short stature treated with rhGH, rhGH+GnRHa or not treated.
- Identify predictors predicting adult height

Hypothesis

- We hypothesized that delaying puberty with GnRHa improves adult height in rhGH treated short children.

Methods

- This is a retrospective study of children assesed for short stature in our clinic between the years 2000 and 2009 (fig.1.).
- Multiple regression analysis was used to identify predictors of adult height.

Inclusion criteria:
- Adolescents that had achieved or were close to achieving adult height (defined as height velocity < 1 cm/year or > 2 years from menarche and that had been investigated for short stature (< -2 SDS) and or relatively early puberty.
- Diagnoses included:
    - GHD (GH_{max} < 10 µg/l either spontaneous secretion overnight and/or after stimulation (most often arginine followed by insulin)
    - SGA (birth weight or length <-2SD lacking post-natal catch up)
    - ISS (Ht SDS <- 2 SDS) with GH_{max} ≥ 10 µg/l and without known etiology

Exclusion criteria:
- Syndromes (e.g. Prader Willi, Noonan syndrome)
- Chromosomal abnormalities (e.g. Turners syndrome)
- Malignancy
- Malnutrition (e.g. celiac disease, hypothyreosis)
- True pubertas praecox (B2 at ≤ 8.5 years of age in girls or testicles > 3ml at ≤ 9.5 years of age in boys)
- Patients with delayed puberty
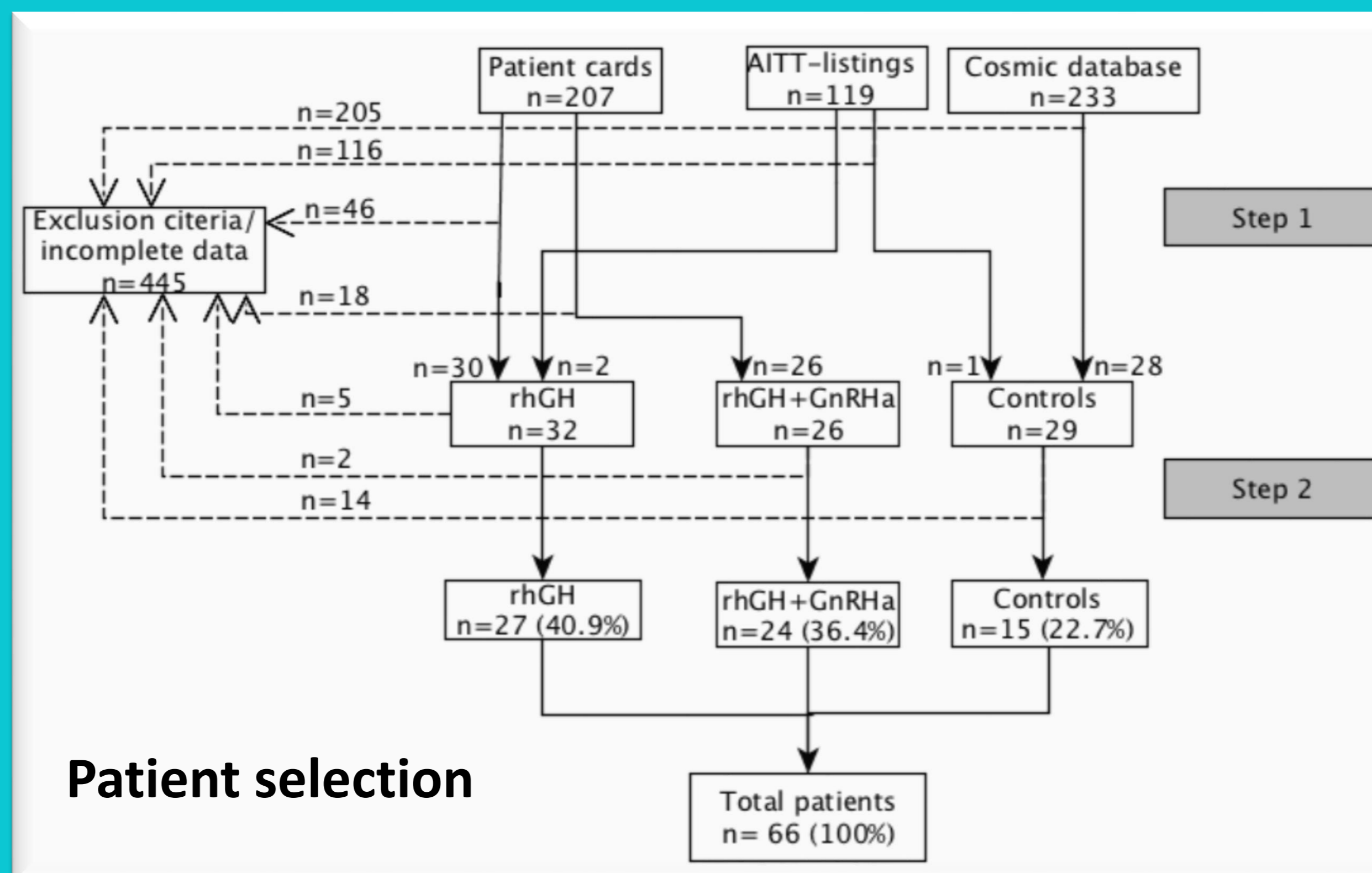

Patient selection

Figure 1. An overview of the identification and selection of patients.

Patient characteristics

Treatment group	rhGH	rhGH+GnRHa	Controls
Patients n (% tot)	27 (40.9)	24 (36.4)	15 (22.7)
Females, n (%)	10 (37)	13 (54.2)	6 (60)
Diagnoses: GHD n(%)	21 (77.8)*	14 (58.3)	----------
Non-GHD n(%)	6 (22.2)	10 (41.6)	15 (100)
Age at baseline	7.6 (3.0)	9.3 (3.0)	11.4 (4.0)
Age GH start	10.1(2.2)	10.9(2.2)	----------
Age GH stop	16.4(2.1)	16.4(1.4)	----------
Years of GH	6.3(2.6)	5.5(2.1)	----------
First year on GH HtV	0.5(0.2)	0.3(0.3)	----------
Age GnRHa start	---------	11.9(2.9)	----------
Age GnRH stop	---------	13.6(3.1)	----------
Years of GnRHa	---------	1.7(1.0)	----------

Values are presented as means (standard deviation). *= p<0.02 vs. controls.
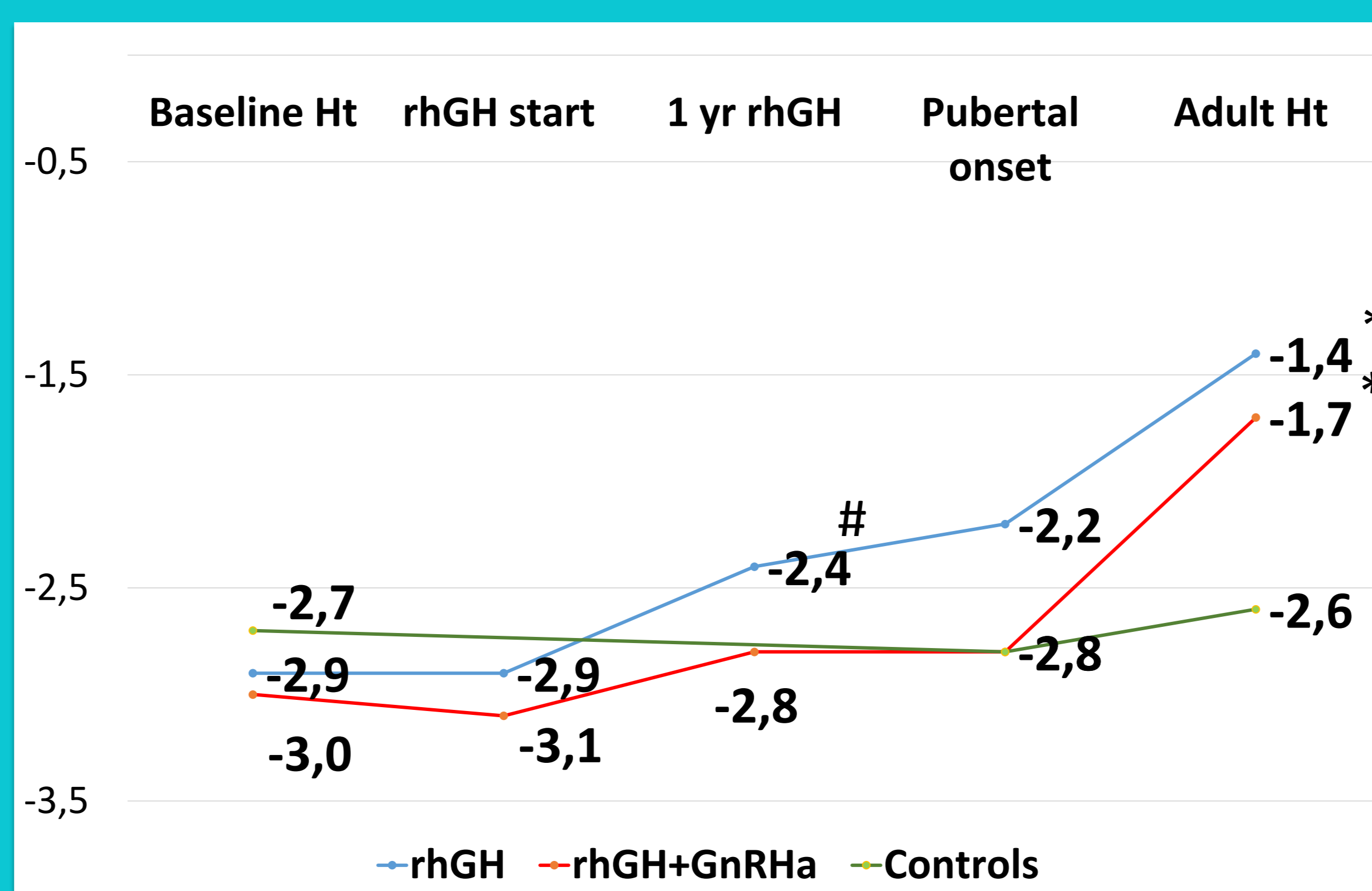Baseline = workup

Height SDS from baseline to adult height

Fig 2. Summary of the changes in height SDS over time for the treatment groups. Values are represented as mean of the treatment group.
#= p<0.05 vs. rHGH+GnRHa and controls, * = p <0.01 vs. controls.

Results

- Mean (SD) adult height was -1.4 (0.9) SDS in rhGH not different from -1.7 (0.6) SDS in rhGH + GnRHa treated patients.
- Adult height in rhGH and rhGH + GnRHa treated patients were significantly higher than -2.6 (0.8) in controls (p<0.01 and p<0.05, respectively).
- The gain from baseline to adult height did not differ between patients treated with rhGH or rhGH + GnRHa but was larger than in non-treated children (p<0.005 and p=0.011, respectively).
- The distance from reference mean age at B2 or testicular volume > 3ml to pubertal start was + 0.7 (later than average), + 0.3 and -1.2 years, in the 3 groups, respectively.
- The most important predictors of adult height were a low baseline height, long distance to MPH and a low GH_{max}.

Conclusions:

- rhGH improves adult height
- rhGH + GnRHa did not further improve adult height
- rhGH or rhGH + GnRHa treatment resulted in greater adult height compered to controls.
- This study does not support that delaying puberty with GnRHa promote adult height in children who enter puberty at average age.

References

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4. van Gool et al. *The journal of Clinical Endocrinology & Metabolism, 2007;* 92(4): 1402-1408.

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