

# Pulsatile GnRH is superior to hCG in therapeutic efficacy in adolescent boys with hypogonadotropic hypogonadism

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## OBJECTIVES

To assess the effectiveness and safety of GnRH or hCG treatment in adolescent boys with hypogonadotropic hypogonadism.

## METHODS

Our enroll criteria includes: boy > 14yr without any sign of puberty, testis < 4ml, BA ≥ 12yr; Sex hormone (LH, FSH, T) are pre-pubertal level; No other hormones problems (other pituitary glands axis are normal except gonad axis); No space occupying lesion, No tumor on MRI of pituitary and hypothalamus area; KS patients may be accompanied with dysosmia or dysplasia of olfactory bulb or olfactory tract on MRI; Karyotype is 46,XY; Exclude chronic diseases, malnutrition. For the boy < 14yr. who accompanied with micropenis or cryptorchid or hypospadias and they have anosmia or dysplasia of olfactory bulb/olfactory sulcus/olfactory tracts on MRI include in; or CHH confirmed by gene test. We also enrolled KS patients when they have testis volume > 4ml or the testosterone level > 200ng/L, accompanied anosmia or dysplasia of olfactory bulb /olfactory sulcus/olfactory tracts on MRI, and the puberty arrested in half a year. 12 patients received 8 to 10 μg of GnRH, subcutaneously injected every 90 min using a pump. 22 patients received hCG, injected intramuscularly as follows: for the first three months, 1000 IU of hCG was injected two times per week, then once every other day for the next three months. The dose of hCG was increased to 2000 IU after 6 month treatment and the above cycle was repeated for another six months. All patients were treated for 12 to 14 months and followed up every 3 months.

Table 1. Patients' baseline parameters in different groups before treatment

| Group   | AA (y)       | H (cm)         | BW (kg)       | BMI          | BA (y)       | BA/CA       | TV(ml)      | PL (cm)     | LH(mIU/liter) |
|---------|--------------|----------------|---------------|--------------|--------------|-------------|-------------|-------------|---------------|
| GnRH    | 13.39 ± 1.66 | 155.90 ± 11.35 | 50.44 ± 17.13 | 20.97 ± 4.61 | 11.50 ± 1.77 | 0.86 ± 0.10 | 2.53 ± 2.07 | 4.74 ± 1.44 | 0.35 ± 0.31   |
| hCG     | 13.89 ± 2.44 | 153.50 ± 9.12  | 47.56 ± 12.14 | 20.01 ± 3.95 | 11.68 ± 1.68 | 0.84 ± 0.94 | 2.15 ± 2.05 | 3.91 ± 1.38 | 0.30 ± 0.34   |
| P value | 0.601        | 0.419          | 0.758         | 0.373        | 0.721        | 0.245       | 0.350       | 0.140       | 0.683         |

Table 1. (Cont'd.)

| Group   | FSH (mIU/liter) | LH/FSH      | T (ng/dl)    | E2 (pg/ml)   | IGF-1(ng/mL)   | IGF-1/IGF-BP3 | HbA1c (%)   | ALP (U/liter)   |
|---------|-----------------|-------------|--------------|--------------|----------------|---------------|-------------|-----------------|
| GnRH    | 1.09 ± 0.68     | 0.32 ± 0.11 | 12.94 ± 6.92 | 18.62 ± 5.41 | 253.00 ± 83.51 | 59.73 ± 15.75 | 5.5 ± 0.18  | 283.51 ± 101.24 |
| hCG     | 0.72 ± 0.43     | 0.36 ± 0.20 | 9.02 ± 5.83  | 15.26 ± 6.47 | 235.24 ± 86.43 | 56.41 ± 12.81 | 5.49 ± 0.22 | 252.01 ± 82.37  |
| P value | 0.101           | 0.963       | 0.231        | 0.375        | 0.962          | 0.809         | 0.730       | 0.320           |

AA, average age; H, height; BW, body weight; BMI, body mass index; BA, bone age; CA, chronological age; TV, testicular volume; PL, penile length; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone; E2, estradiol E2; IGF-1, insulin-like growth factor 1; IGF-BP3, IGF binding protein 3; HbA1c, hemoglobin A1c; ALP, alkaline phosphatase.

Table 4. Comparison of blood chemical levels between two treatments

| Parameter       | Group | Treatment Time (months) |                 |                 |
|-----------------|-------|-------------------------|-----------------|-----------------|
|                 |       | 0                       | 6               | 12              |
| BA (years)      | GnRH  | 11.50 ± 1.77            | 11.89 ± 1.97    | 12.73 ± 2.0#    |
|                 | hCG   | 11.68 ± 1.68            | 12.04 ± 1.74    | 12.81 ± 1.53#   |
| BA/CA           | GnRH  | 0.86 ± 0.10             | 0.82 ± 0.19     | 0.83 ± 0.12     |
|                 | hCG   | 0.84 ± 0.94             | 0.81 ± 0.23     | 0.84 ± 0.19     |
| ALP (μ/liter)   | GnRH  | 283.51 ± 101.24         | 354.73 ± 101.54 | 346.83 ± 62.95# |
|                 | hCG   | 252.01 ± 82.37          | 373.86 ± 94.42  | 351.63 ± 73.84# |
| IGF-1 (n/liter) | GnRH  | 253.00 ± 83.51          | 334.45 ± 83.75  | 368.35 ± 83.75# |
|                 | hCG   | 235.24 ± 86.43          | 326.64 ± 73.83  | 359.65 ± 69.73# |
| IGF-1/IGF-BP3   | GnRH  | 59.73 ± 15.75           | 70.63 ± 13.71   | 62.42 ± 19.64#  |
|                 | hCG   | 56.41 ± 12.81           | 63.51 ± 15.55   | 70.63 ± 20.52#  |
| HbA1c (%)       | GnRH  | 5.5 ± 0.18              | 5.51 ± 0.42     | 5.28 ± 0.52     |
|                 | hCG   | 5.49 ± 0.22             | 5.81 ± 0.74     | 5.51 ± 0.94     |

BA, bone age; CA, chronological age; ALP, alkaline phosphatase; IGF-1, insulin-like growth factor 1; IGF-BP3, IGF binding protein 3; HbA1c, hemoglobin A1c. #, significantly different compared to 0 month, same group, P < 0.05.

Table 5. Comparisons of therapeutic efficacy between different treatments (mean ± SD)

| Type of HH | Group 1      |             |               |                 |                 | Group 2       |             |             |               |                 |                 |               |
|------------|--------------|-------------|---------------|-----------------|-----------------|---------------|-------------|-------------|---------------|-----------------|-----------------|---------------|
|            | TV (mL)      | PL (cm)     | LH(mIU/liter) | FSH (mIU/liter) | T(ng/dL)        | E2 (pg/mL)    | TV(mL)      | PL (cm)     | LH(mIU/liter) | FSH (mIU/liter) | T(ng/dL)        | E2 (pg/mL)    |
| KS         | 12.87 ± 5.48 | 7.57 ± 2.59 | 5.45 ± 2.58   | 6.47 ± 2.43     | 328.92 ± 134.45 | 26.42 ± 11.42 | 5.15 ± 1.28 | 6.33 ± 2.34 | 0.61 ± 1.51   | 0.96 ± 1.03     | 215.36 ± 147.59 | 19.88 ± 13.57 |
| nIHH       | 14.52 ± 4.47 | 9.02 ± 3.47 | 6.93 ± 2.46   | 9.86 ± 3.47     | 245.02 ± 211.85 | 21.31 ± 7.36  | 6.93 ± 2.17 | 7.09 ± 1.67 | 0.82 ± 1.43   | 0.72 ± 1.46     | 174.34 ± 132.48 | 28.09 ± 18.46 |
| P value    | 0.213        | 0.202       | 0.178         | 0.561           | 0.109           | 0.417         | 0.494       | 0.761       | 0.542         | 0.736           | 0.250           |               |

TV, testicular volume; PL, penile length; FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, estradiol E2; T, testosterone. Group 1, GnRH treatment; Group 2, hCG treatment.

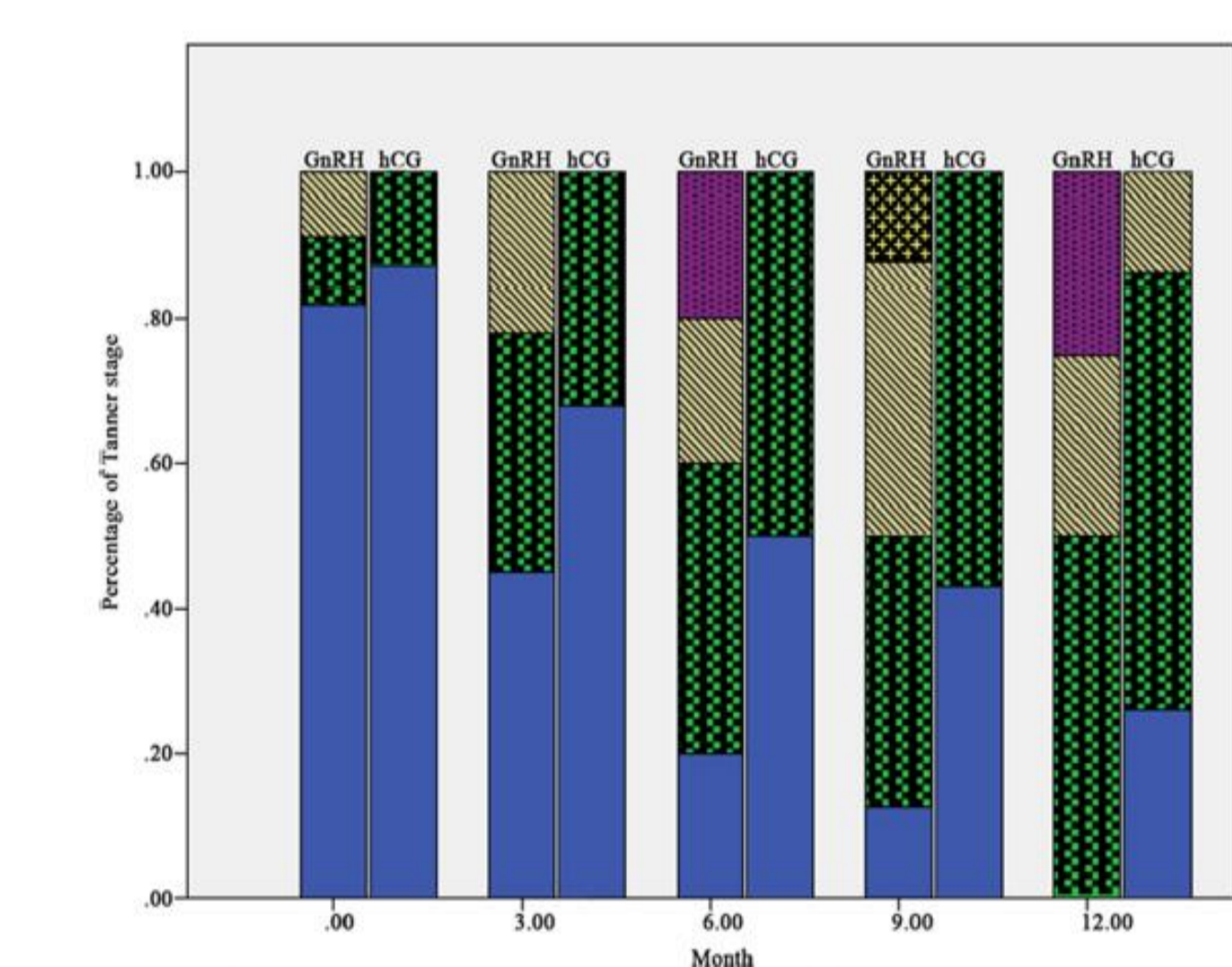


Figure 1. Percentages of patients at different Tanner stages in group 1 and group 2.

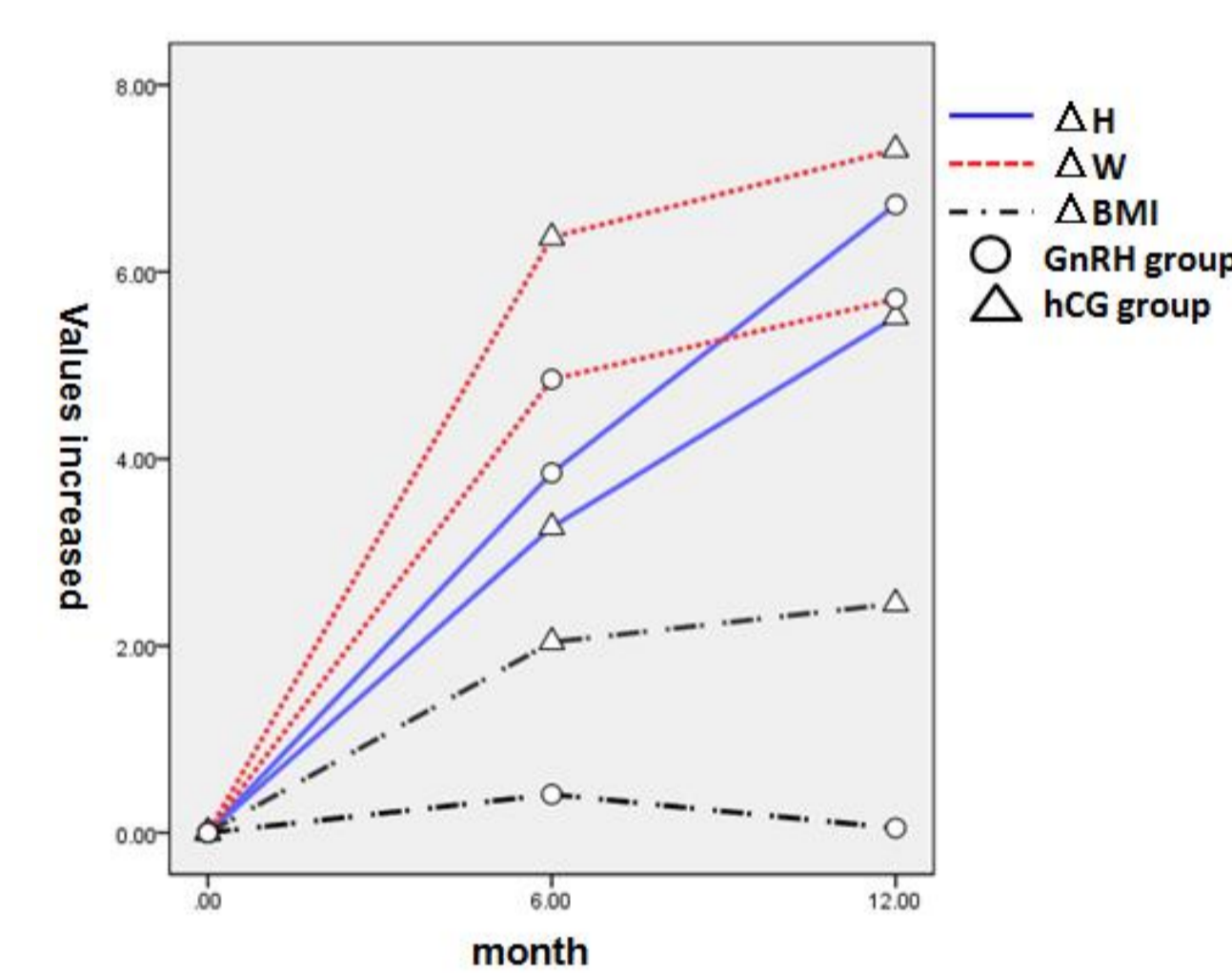


Figure 2. Comparison of physical status between two treatments

Table 2. Comparisons of therapeutic effects between two treatments

| Variable       | Group | Treatment time (month)    |                |                 |                 |                  |
|----------------|-------|---------------------------|----------------|-----------------|-----------------|------------------|
|                |       | 0                         | 3              | 6               | 9               | 12               |
| TV (mL)        | GnRH  | 2.53 ± 2.07               | 7.043 ± 3.04   | 9.21 ± 3.14*    | 11.24 ± 3.35*   | 13.09 ± 3.82*#   |
|                | hCG   | 2.15 ± 2.05               | 4.21 ± 1.42    | 4.83 ± 1.82     | 5.531 ± 1.61    | 6.01 ± 1.33      |
| PL (cm)        | GnRH  | 4.74 ± 1.44               | 5.94 ± 1.97    | 6.03 ± 2.25     | 7.01 ± 1.47     | 8.03 ± 1.24#     |
|                | hCG   | 3.91 ± 1.38               | 5.31 ± 1.23    | 5.31 ± 1.04     | 6.29 ± 1.28     | 6.03 ± 1.10#     |
| LH (IU/liter)  | GnRH  | 0.35 ± 0.31               | 4.39 ± 3.31*   | 5.38 ± 3.14*    | 4.02 ± 1.35*    | 5.02 ± 0.75*#    |
|                | hCG   | 0.30 ± 0.34               | 0.50 ± 1.14    | 0.22 ± 0.41     | 2.31 ± 2.57     | 0.62 ± 0.85      |
| FSH (IU/liter) | GnRH  | 1.09 ± 0.68               | 6.57 ± 5.02*   | 9.76 ± 11.13*   | 4.51 ± 0.42*    | 7.02 ± 1.04*#    |
|                | hCG   | 0.72 ± 0.43               | 0.55 ± 0.46    | 0.86 ± 1.14     | 2.03 ± 2.16     | 0.82 ± 1.13      |
| T (nmol/liter) | GnRH  | 12.94 ± 6.92 <sup>§</sup> | 123.87 ± 95.47 | 161.02 ± 103.42 | 273.42 ± 102.32 | 278.94 ± 134.53# |
|                | hCG   | 9.02 ± 5.83 <sup>§</sup>  | 95.42 ± 84.23  | 150.33 ± 62.53  | 153.48 ± 108.53 | 173.32 ± 132.53# |
| E2 (ng/liter)  | GnRH  | 18.62 ± 5.41              | 23.22 ± 11.48  | 29.85 ± 14.53   | 26.54 ± 6.47    | 25.73 ± 9.65     |
|                | hCG   | 15.26 ± 6.47              | 24.53 ± 6.23   | 23.64 ± 12.74   | 25.52 ± 11.47   | 23.54 ± 12.74    |

TV, testicular volume; PL, penile length; LH, luteinizing hormone; FSH, follicle stimulating hormone; T, testosterone; E2, estradiol E2. #, significantly different compared to 0 month, same group, P < 0.05; \*, significantly different between the two groups, same time point, P < 0.05; §, significantly different from the other time points, same group, P < 0.01.

Table 3. Comparison of physical status between two treatments

| Parameter                | Group | Reference values | Treatment Time (months) |                 |
|--------------------------|-------|------------------|-------------------------|-----------------|
|                          |       |                  | 6                       | 12              |
| H (cm)                   | GnRH  | 155.90 ± 11.35   | 160.05 ± 10.42          | 162.85 ± 12.63# |
|                          | hCG   | 153.50 ± 9.12    | 156.39 ± 13.74          | 159.15 ± 17.03# |
| BW (kg)                  | GnRH  | 50.44 ± 17.13    | 55.97 ± 11.04           | 57.02 ± 11.85   |
|                          | hCG   | 47.56 ± 12.14    | 49.37 ± 11.53           | 54.84 ± 13.38   |
| BMI (kg/m <sup>2</sup> ) | GnRH  | 20.97 ± 4.61     | 21.95 ± 5.29            | 20.94 ± 4.42    |
|                          | hCG   | 20.01 ± 3.95     | 21.94 ± 3.23            | 21.83 ± 6.52    |

H, height; BW, body weight; BMI, body mass index.

#, significantly different compared to 0 month, same group, P < 0.05.

Reference value was from the Percentage Chart of Chinese Children Height and Bodyweight, age 2–18 yr (2005).

## RESULTS

Patients treated with GnRH showed larger testes than those treated with hCG. Patients in both groups showed significantly increased length of penis and testosterone levels. But the difference of two groups was not statistically significant. There was no significant difference in side effects in both groups.

## CONCLUSIONS

Boys with HH maybe effectively treated with GnRH. We suggested that GnRH exhibits higher efficacy in treating adolescent boys with HH than hCG.

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