GH in Turner syndrome

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Outline

- ***Causes of short stature in TS.***
- ***Is GH testing needed?***
- ***Monitoring of Growth in TS.***
- ***Timing of GH initiation.***
- ***Dosing of GH.***
- ***Efficasy of GH treatment.***
- ***Benefits of GH in TS.***
- ***Side effects of GH treatment.***
- ***Duration of GH treatment .***
- ***GH treatment outcome in TS.***

Short stature

- ***Seen in nearly all patients .***
- ***Due to haplo-insufficiency of SHOX gene on the chromosome or abnormal GH /IGF1/IGFBP3 axis.***
- ***GH secretion is preserved in TS and provocative GH testing is usually not required.***

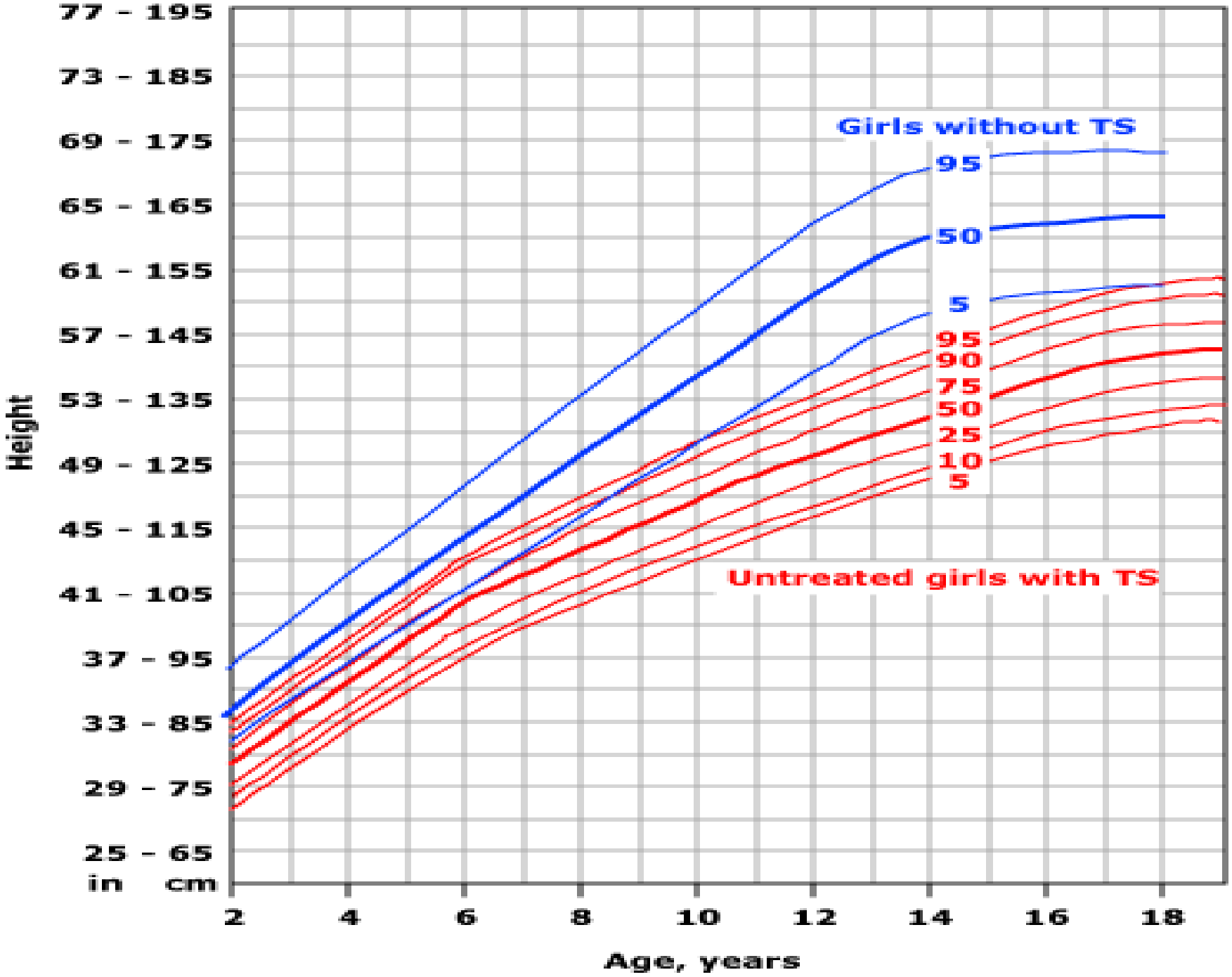
MANAGEMENT OF SHORT STATURE

Monitoring growth :

- ***The height of patients with Turner syndrome should be plotted on growth curves specific for this disorder.***

- ***These growth curves show height percentiles for untreated patients with Turner syndrome, as well as height percentiles for the general female population.***

- ***GH therapy in pharmacologic doses improves growth.***


77 – 195
73 – 185
69 – 175
65 – 165
61 – 155
57 – 145
53 – 135
49 – 125
45 – 115
41 – 105
37 – 95
33 – 85
29 – 75
25 – 65
in cm
Height
Girls without TS
95
50
5
95
90
75
50
25
10
5
Untreated girls with TS
2
4
6
8
10
12
14
16
18
Age, years

Growth hormone therapy

- ***Most** patients should be treated with GH to maximize their **adult height** and improve **body composition.***

Indications and timing

- ***GH should be initiated as soon as the height of a girl with TS falls below the fifth percentile for age on the normal female growth chart(between two and five years of age) .***

- ***Young patients with particularly slow growth velocity may benefit from starting growth hormone even earlier (before the height falls below the fifth percentile).***

Indications and timing

- ***The clinician should monitor how the patient's growth compares with the expected growth based on the mid-parental (target) height and expected target height growth curve.***

- ***Significant deviation from the expected growth curve should prompt assessment of superimposed secondary causes of growth failure and/or earlier intervention.***

Dosing

- In the United States, a typical initial dose of GH is 50 micrograms/kg/day (0.35 to 0.375 mg/kg/week), given once daily .

- Patients with TS are typically treated with somewhat higher doses of GH compared with patients with GH deficiency.

Dosing

- ***Doses of growth hormone up to 67 micrograms/kg/day have been used in the United States.***

- ***GH therapy should be continued until little growth potential remains (BA exceeds 13.5 to 14 years and growth slows to less than 2.5 cm per year).***

Dosing

- ***Because this dosing scheme is based on BW, GH dose may be excessive if the child is overweight.***

- ***To avoid this problem, we suggest measuring serum concentrations of IGF-1 annually .***

- ***GH dose could then be adjusted as needed to maintain IGF-1 below +2 SD above the mean for age and/or Tanner stage of pubertal development, but ideally slightly above the mean (approximately +1 SD).***

Dosing

- ***This is because a high IGF-1 (eg, >+3 SD) may be associated with toxicity, while a low IGF-1 suggests that the dose of GH may be insufficient and may not achieve an optimal growth response.***

DOSING

- ***GH dosing in Turner syndrome patients can be calculated based on body surface area (1.33 mg/m2/day as a starting point).***

- ***This approach may be most appropriate for the TS patients beyond 9 to 10 years of age, when they are more likely to be overweight and body weight-based dosing is more likely to lead to overdosing .***

Efficacy

- ***Initiation of GH at a young age (four to six years) often permits attainment of normal adult height.***

- ***GH therapy improve adult height by 5–8 cm in several randomized trials and observational studies.***

- ***The efficacy is variable and depends on multiple factors including mid-paren-tal height, age at initiation of GH therapy, duration and dose of GH therapy and baseline height prior to initiation of GH therapy.***

Efficacy

- ***Early GH treatment** can correct growth failure and normalize height in **infants and toddlers** with Turner syndrome.*

- ***The effects of this approach on adult height have not been published yet.***

Early usage of Estrogen

- ***We do not recommend the routine use of very low-dose estrogen in prepubertal children (before 11 years of age), because its effects on height are modest (an additional 2.1 cm), and this may be insufficient to justify its use.***

- ***It is possible that such very low-dose estrogen therapy may also improve bone mineralization and memory and cognitive function, but these outcomes require further investigation .***

Efficacy

- *GH therapy may have beneficial effects on body composition.*
- *Increase lean body mass and decreased body fat .*
- *These changes were independent of estrogen exposure.*
- *Do not have a deleterious effect on BP, LVF, or aortic diameter .*

Efficacy

- ***There is conflicting evidence on whether GH therapy worsens the already inherent risk of glucose intolerance in TS.***

- ***It is recommended to monitor Hb A1c annually regardless of GH therapy.***

Efficacy

- ***Adverse effects of GH therapy, intracranial hypertension, scoliosis, slipped capital femoral epiphyses, and pancreatitis are uncommon but perhaps slightly more prevalent than in children who are treated with GH for indications other than TS.***

- ***Height should be monitored every 3–4 months in the first year of therapy and every 4–6 months thereafter .***

Strategies for severe short stature :

- ***In girls 10 to 12 years of age with severe short stature, we suggest offering either treatment with oxandrolone (a nonaromatizable androgen) or delayed pubertal induction, but not both, in addition to growth hormone therapy .***

Adjunctive oxandrolone

- ***Adjunctive oxandrolo Oxandrolone improves height velocity through its anabolic effects (by increasing protein synthesis, lean body mass, and BMD).***

- ***Given at a low dose (0.03 mg/kg per day or less, and increased to no more than 0.05 mg/kg per day) from the age of 10 years or older and in combination with GH therapy.***

Adjunctive oxandrolone

- ***Oxandrolone therapy may improve adult height by 2–5 cm when used concomitantly with GH therapy.***

- ***Higher doses of oxandrolone should not be used, because they may result in virilization.***

- ***Oxandrolone treatment is continued until estradiol therapy is begun, around 11 or 12 years of age.***

cont

- ***Either of these approaches results in a similar degree of improvement in adult height.***

- ***Further study is needed to evaluate which girls with Turner syndrome would benefit most from combination therapy with GH and oxandrolone and to determine the optimal duration of this treatment***

Delayed pubertal induction

- ***May improve height outcome** by postponing epiphyseal fusion triggered by estradiol, and may be helpful when combined with high-dose growth hormone .*

- *If this approach is chosen, monotherapy with GH is continued, and estrogens **are started closer to 14 years** rather than the more typical time point of **11 to 12 years** of age.*

- *This results in delayed induction of puberty and permits additional growth before epiphyseal fusion.*

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Childhood growth hormone treatment in women with Turner syndrome - benefits and adverse effects

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GH outcome

- ***Medical records and biochemical findings of 33 TS women treated with GH in childhood (GH+) were compared to those of 124 TS women who did not receive GH (GH–).***

- ***GH+ women were significantly taller and had a better lipid profile and lower prevalence of arterial hypertension than GH– .***

- ***They also had lower thrombocyte counts, a greater prevalence of retrognathism and nail anomalies, especially when the GH treatment was delayed.***

GH outcome

- ***Long-term GH use** was **not** as **effective** for growth as GH treatment during the initial period and seemed to have resulted in elevated creatinine levels.*

- ***GH treatment in childhood has benefits in adulthood but adverse effects may occur, especially in individuals with treatment that is **delayed** or is **too long**.***

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting

in European Journal of Endocrinology

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*(Details of the International Turner Syndrome Consensus Group is presented in the Summary section)

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GH outcome

- ***Data indicate that height gain of about 1 cm per year of GH therapy is a reasonable expectation.***

- ***Two European studies using high GH doses at young ages have demonstrated much more dramatic gains of 15–17 cm (mean) vs baseline projected AH .***

GH outcome

- *If catch-up growth to within the normal range occurred within the first two years of treatment, HV was maintained close to the mean for age, and there was adequate pubertal growth, and then AH within the lower normal range (above 152 cm) was observed.*

- *Various lines of evidence indicate that younger age at treatment initiation at least 4 years of treatment prior to puberty is associated with greater treatment effect.*

GH outcome

- ***Whether the risk of T2DM is increased by GH treatment in TS remains an open question.***

Fertility preservation in Turner syndrome

- ***Fertility preservation is potentially feasible in women with TS, as many girls with TS have ovarian follicles until their late teens, and some women with mosaic TS have follicles for many years thereafter, even though they tend to experience early menopause .***

- ***Oocyte cryopreservation after controlled ovarian hyperstimulation is a possible fertility preservation option in young mosaic TS women with persistent ovarian function.***

Fertility preservation in Turner syndrome

- ***Case reports describe cryopreservation of 8–13 mature oocytes after controlled ovarian hyperstimulation in TS women aged 14–28 years.***
- ***So far, there are no pregnancies reported after oocyte freezing and thawing in TS, as these women are still young and have not attempted pregnancy yet.***
- ***Vitrification of oocytes at an even younger age, perhaps about 12 years, may be feasible, but so far, there are no reliable data in TS .***

Fertility preservation in Turner syndrome

- ***Biopsy of ovarian cortical tissue** is feasible at younger ages, but it requires an operation and anesthesia.*
- *In a study of follicular density in TS girls, the youngest girl studied was **8 years old**, but she had very small ovaries with no follicles .*
- *Signs of spontaneous puberty, mosaicism, and normal FSH and AMH concentrations for age and pubertal stage were positive and statistically significant, but not exclusive, prognostic factors to find follicles.*
- *To date, there is **not enough evidence** to recommend routine fertility preservation of young TS girls **before** the age of **12 years .***


Thanks