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# Somatropin for Turner Syndrome

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Rapid Review

## Table of Contents

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<b>Abbreviations</b> .....	<b>4</b>
<b>Key Messages</b> .....	<b>5</b>
<b>Context and Policy Issues</b> .....	<b>5</b>
<b>Research Question</b> .....	<b>6</b>
<b>Methods</b> .....	<b>6</b>
Literature Search Methods .....	6
Selection Criteria and Methods .....	6
Exclusion Criteria.....	7
Critical Appraisal of Individual Studies .....	7
<b>Summary of Evidence</b> .....	<b>7</b>
Quantity of Research Available.....	7
Summary of Study Characteristics.....	7
<b>Summary of Critical Appraisal</b> .....	<b>8</b>
Summary of Findings .....	10
<b>Limitations</b> .....	<b>13</b>
<b>Conclusions and Implications for Decision- or Policy-Making</b> .....	<b>13</b>
<b>References</b> .....	<b>15</b>
<b>Appendix 1: Selection of Included Studies</b> .....	<b>16</b>
<b>Appendix 2: Characteristics of Included Publications</b> .....	<b>17</b>
<b>Appendix 3: Critical Appraisal of Included Publications</b> .....	<b>18</b>
<b>Appendix 4: Main Study Findings</b> .....	<b>20</b>
<b>Appendix 5: Other Relevant Guidelines</b> .....	<b>25</b>
<b>Appendix 6: References of Potential Interest</b> .....	<b>26</b>

## List of Tables

---

Table 1: Selection Criteria.....	6
Table 2: Characteristics of Included Guideline From the 2016 Cincinnati International Turner Syndrome Meeting, Gravholt et al.(2017) <sup>9</sup> .....	17
Table 3: Strengths and Limitations of the Guideline From the 2016 Cincinnati International Turner Syndrome Meeting, Gravholt et al.(2017) <sup>9</sup> Using AGREE II <sup>8</sup> .....	18
Table 4: Summary of Recommendations of the Guideline From the 2016 Cincinnati International Turner Syndrome Meeting, Gravholt et al. (2017) <sup>9</sup> .....	20
Table 5: Characteristics of Other Guideline (GRS Perspective, 2019) <sup>11</sup> .....	25

## List of Figures

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Figure 1: Selection of Included Studies .....	16
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## Abbreviations

<b>GH</b>	growth hormone
<b>GRADE</b>	Grading of Recommendations, Assessment, Development, and Evaluations
<b>IGF-I</b>	insulin-like growth factor – I
<b>TS</b>	Turner syndrome

## Key Messages

- Early initiation of growth hormone therapy is recommended in children with Turner syndrome if the child already has growth failure or has a high chance of short stature (1 guideline).
- Growth hormone treatment can be started at 45 mcg/kg/day to 50 mcg/kg/day (1 guideline).
- Monitor treatment by regular height measurements and assessment of levels of insulin-like growth factor-I (1 guideline).
- Continue treatment until the desired height is achieved or when no more growth potential remains (1 guideline).

## Context and Policy Issues

Turner syndrome (TS) is a chromosomal abnormality in female individuals in which the X chromosome is partially or completely absent. TS occurs due to the deletion or nonfunctioning of 1 of the X chromosomes in the female embryo.<sup>1</sup> It affects approximately 1 in 2,500 female live births.<sup>2</sup> Also known as congenital ovarian hypoplasia syndrome;<sup>3</sup> TS presents as a spectrum of clinical features affecting multiple organ systems. Primarily TS is associated with premature ovarian failure resulting in absent or delayed puberty and infertility.<sup>3</sup> The most common feature of TS is growth failure resulting in short stature, often noticeable by age 5.<sup>1</sup> Children with TS are typically born with a birth length and weight in the low normal range. However, the growth rate in the early years for those with TS is slower than their peers without TS and decreases severely around puberty. Without treatment, their average adult height is around 20 cm shorter than people without TS.<sup>2</sup> Other than the shorter stature, the characteristic facial features of TS include hypertelorism (increased distance between the eyes), webbed neck, high arched palate, and low-set ears. TS is also associated with a higher risk of cardiovascular malformations (e.g., coarctation of the aorta, bicuspid aortic arch), endocrine and metabolic dysfunction (e.g., thyroiditis, glucose intolerance, diabetes, dyslipidemia), musculoskeletal features (e.g., scoliosis, Madelung's deformity, low bone mineral density), and other gastrointestinal and renal impairments.<sup>4</sup> TS can be suspected in utero (during prenatal ultrasounds) or at birth based on clinical features. Diagnosis is confirmed with karyotype testing.<sup>1</sup> Later in childhood or adolescence, a patient can present with short stature, delayed onset of puberty or an absence of menstrual periods. The mainstay of management of TS is growth promotion using growth hormone (GH) with or without oxandrolone, estrogen replacement, and managing the spectrum of clinical and metabolic concerns.<sup>4</sup>

Short stature in TS is due to the haploinsufficiency of the *SHOX* gene located in the X chromosome.<sup>5</sup> The *SHOX* deficiency also causes the various musculoskeletal and craniofacial impairments associated with TS. While there is no true GH deficiency in TS, patients benefit from GH therapy.<sup>2</sup>

GH is a peptide hormone naturally produced by the anterior pituitary gland and induces linear growth in children.<sup>5</sup> Synthetic or recombinant human GH, somatropin, has been used to treat short stature in children and adults due to various causes. Somatropin products approved in Canada for promoting growth in children with TS are Genotropin, Humatrope, Nutropin, Omnitrope,<sup>6</sup> and Saizen.<sup>7</sup> A 2014 CADTH reimbursement

review of Genotropin found that treatment with somatropin results in greater and rapid height gain, and final height in children with TS whose epiphyses have not closed.<sup>7</sup> The Canadian Drug Expert Committee (CDEC) recommended listing Genotropin in this population.<sup>7</sup>

Evidence-based guidelines regarding best practices could help inform policy decisions regarding reimbursement criteria for somatropin in children with TS. The purpose of the current report is to summarize the evidence-based guidelines regarding the use of GH therapy in children with TS.

## Research Question

What are the evidence-based guidelines regarding the use of growth hormone therapy for children with Turner syndrome?

## Methods

### Literature Search Methods

An information specialist conducted a literature search on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, and a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were human growth hormone and Turner Syndrome. [CADTH-developed search filters](#) were applied to limit retrieval to guidelines. The search was completed on June 13, 2023 and limited to English-language documents published since January 1, 2013.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

**Table 1: Selection Criteria**

Criteria	Description
Population	Children (< 18 years old) with Turner syndrome
Intervention	All somatropin products
Comparator	Not applicable
Outcomes	Recommendations regarding best practices (e.g., dose and timing of treatment, duration of treatment, laboratory cut-offs for eligibility, monitoring treatment response)
Study designs	Evidence-based guidelines

## Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#), were duplicate publications or were published before 2013.

Guidelines with unclear methodology but relevant to the research question were excluded from the main report, but their characteristics and findings are presented in [Appendix 5](#).

## Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument<sup>8</sup> for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 154 citations were identified in the literature search. Following screening of titles and abstracts, 130 citations were excluded, and 24 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search or via handsearching for a full-text review. Of these potentially relevant articles, 24 publications were excluded for various reasons, and 1 evidence-based guideline<sup>9</sup> met the inclusion criteria and was included in this report. [Appendix 1](#) presents the PRISMA<sup>10</sup> flow chart of the study selection.

We also found a perspective document from the Growth Hormone Research Society (GRS).<sup>11</sup> It was not considered an evidence-based guideline but provided content relevant to the research question. The characteristics and relevant recommendations from this publication are presented in [Appendix 5](#). Additional references of potential interest are provided in [Appendix 6](#).

### Summary of Study Characteristics

We included 1 evidence-based guideline, namely the clinical practice guideline<sup>9</sup> from the 2016 Cincinnati International Turner Syndrome Meeting, in this report. It provides recommendations regarding various care areas for people with TS such as, diagnosis and genetics, growth and puberty, reproductive care and pregnancy, transition from pediatric to adult care, other health concerns, and health surveillance. Relevant to the current report, we have summarized the recommendations related to GH therapy in the sections below.

Additional details regarding the characteristics of included publications are provided in [Appendix 2](#).

### Study Design

The clinical practice guideline<sup>9</sup> published in 2017, was initiated by the European Society of Endocrinology (Europe) and the Pediatric Endocrine Society (US), collaborating with several other professional societies from Europe and the US. The guideline development working group consisted of endocrinologists and

clinicians from other specialties, along with an epidemiologist, and a clinical psychologist. A patient advocate was also involved in the meetings.

Recommendations were developed and finalized through 2 working group meetings. The working group identified 4 clinical questions, with separate inclusion criteria and outcomes of interest. They conducted systematic literature searches for these questions and used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework to evaluate the evidence and formulate the recommendations. Factors such as quality of evidence, a risk-benefit profile, and values and preferences such as patient perspectives and implementation feasibility were considered in this process. Other recommendations were based on the majority consensus of the working group. The strength of each recommendation was indicated in the verbiage: “recommend” and “suggest” for strong and weak recommendations, respectively. The quality of evidence for each recommendation was ranked from strong to very low, following the GRADE format.

The clinical question from this guideline relevant to the current report was “what is the effect of growth-promoting treatment in TS?”<sup>9</sup>. A systematic literature search and formal GRADE assessment was conducted for this question. Randomized controlled trials published since 1990, which examined the effectiveness of GH therapy with or without oxandrolone were searched for. Thus, 24 publications were included, in which 12 were about GH therapy. Characteristics of these included studies were reported in the publication.

### **Country of Origin**

The guideline<sup>9</sup> was developed for the US and European countries.

### **Patient Population**

The target population of this guideline are children, adolescents, and adults with TS. The population relevant to the current report are children (< 18 years of age) with TS.<sup>9</sup>

The intended users of the guideline are health care providers of individuals with TS, including primary care and specialized care (e.g., endocrinologists, fertility specialists, geneticists).<sup>9</sup>

### **Interventions and Comparators**

The guideline provided recommendations regarding various interventions for diagnosing and caring for individuals with TS.<sup>9</sup> The intervention relevant to the current report was GH therapy with or without concomitant treatment with oxandrolone and estrogen.

### **Outcomes**

The relevant outcomes considered in the guidelines related to growth-promoting treatments were height, quality of life, mortality, cardiovascular adverse effects, and masculinization.<sup>9</sup>

## **Summary of Critical Appraisal**

In this section, we have provided a summary of methodological strengths and limitations of the included guideline.<sup>9</sup> Additional details are provided in [Appendix 3](#).



The scope and purpose of the included guideline were clearly described. The objective of the guideline and the health questions covered were clear. The target population and the intended users of the guideline were clear from the publication. The guideline development working group included clinicians from various relevant specialties, a psychologist, and an epidemiologist. While patient partners were not directly involved in guideline development, patient advocacy group members participated in the working group meetings and reviewed the draft.

Recommendations were either based on evidence identified through systematic searches or based on expert opinion. Systematic literature searches were conducted for 4 specific clinical questions considered by the working group. Study inclusion criteria and outcomes of interest for each of these questions were reported. For these questions, evidence was evaluated using the GRADE framework, and recommendations were evidence based. Multiple electronic databases were searched. Since the search methods, such as search strategy, were not reported, we could not ascertain whether the searches were robust and could capture all relevant literature. Study selection (as a flow chart) and characteristics of included studies were reported with adequate details. The strength and limitations of the evidence base were described. However, many of the other recommendations provided in the guideline were based on the expertise and opinion of the working group and developed through consensus. Supporting evidence was not provided for all of them, and it was unclear whether systematic searches were conducted to identify evidence.

One clinical question from the guideline (“What is the effect of growth-promoting treatment in TS?”)<sup>9</sup> was relevant to the current report. A systematic literature search of multiple databases was conducted to identify evidence for this question. Of the 9 recommendations from the guideline related to GH therapy, 3 were based on formal GRADE assessments. The authors discussed some evidence related to 2 of the recommendations, and supporting evidence was not reported for 4 of the relevant recommendations. It was unclear whether this was due to a lack of evidence or a limited literature search. The recommendations based on expert opinion were not identifiable from the evidence-based recommendations. Thus, even though systematic searches were conducted for the relevant research question, the limitations around reporting methodology made interpretation challenging.

The recommendation statements were specific, unambiguous, and easily identifiable. The strength of each recommendation and the quality of supporting evidence were given clearly. However, the reason why a specific recommendation was rated as strong versus weak was unclear. Similarly, while the quality of evidence (ranging from strong to very low quality) was provided, details of evidence such as the number of relevant studies, and findings from them were not always clear. Authors reported that quality of evidence, risk-benefit profile, and values and preferences were considered while formulating the recommendations.

Experts reviewed the draft guideline before publication. Feedback received from external review and from professional societies were addressed appropriately and were made available with the publication. A procedure for updating the guidelines was not provided. There was no advice and/or tools to help implement the recommendations, as well as to audit or monitor adherence to recommendations. The guideline did not discuss the potential resource implications of applying the recommendations.

Lastly, the guideline likely had editorial independence. Potential conflicts of interest of the working group members were reported and available for review. It is unlikely that the funding body influenced the contents of the guideline.

## Summary of Findings

We have summarized the relevant recommendations along with the supporting evidence (if available) from the clinical practice guideline from the 2016 Cincinnati International Turner Syndrome Meeting<sup>9</sup> in this section. [Appendix 4](#) presents the detailed recommendation statements, supporting evidence, and authors' comments.

### Guidelines Regarding the Use of Growth Hormone Therapy in Children With Turner Syndrome

#### *Initiation of GH Therapy*

The Cincinnati International Turner Syndrome Meeting<sup>9</sup> guidelines recommend initiating GH therapy early at 4 to 6 years of age (preferably before 12 to 13 years) if,

- the child has growth failure, as evidenced by a height velocity below the 50th percentile over a period of 6 months and no other treatable causes of poor growth, or
- child is already short for age or has a high chance of short stature (short parents and short predicted pubertal height).

Strong recommendation based on moderate quality evidence from 14 randomized controlled trials.<sup>9</sup> The supporting evidence demonstrated that with GH therapy, a height gain of 1 cm per year can be expected (10 studies). High doses at younger ages can result in height gains of up to 15 to 17 cm than their predicted adult height without GH (2 studies). The authors noted that the main limitations of evidence were high heterogeneity, lack of adequate blinding, high loss to follow-up, and unclear outcome definitions.

The guideline authors provided some comments regarding the discontinuation of GH therapy but did not provide formal recommendations. Treatment can be continued until a desired height is achieved or when there is no more growth potential remaining, as evidenced by bone age greater than 14 years and a height velocity of less than 2 cm per year (evidence unclear). After completion of puberty, treatment can be discontinued as there is no physiological rationale for continuing (evidence unclear).

#### *Dose and Frequency of GH Therapy*

Recommended GH dose:

- 45 mcg/kg/day to 50 mcg/kg/day
- 1.3 mg/m<sup>2</sup>/day to 1.5 mg/m<sup>2</sup>/day (4.0 to 4.5 IU/m<sup>2</sup>/day)
- can be increased to 68 mcg/kg/day if adult height potential is considerably low.

Strong recommendation based on strong evidence.<sup>9</sup> However, details of the supporting evidence were unclear from the publication.

Authors noted that higher doses are only warranted if the height prognosis is very poor. However, further details on the factors that might indicate a 'very poor' prognosis were unclear. Potential risks and benefits of treatment should be discussed with the patient when giving higher doses.

### ***Treatment Monitoring***

The guidelines provided recommendations for regular height measurements and IGF-I monitoring to assess treatment response, and to adjust GH dose.

#### **Height Measurement:**

- every 4 to 6 months during the first year of treatment
- at least every 6 months thereafter.

Strong recommendation based on moderate quality evidence.<sup>9</sup> However, details of the supporting evidence were unclear from the publication.

#### **IGF-I Measurement:**

- IGF-I should be measured at least once a year.

Strong recommendation based on low-quality evidence.<sup>9</sup> However, details of the supporting evidence were unclear from the publication.

#### **IGF-I Levels:**

- measured IGF-I levels should be less than or equal to 2 standard deviations (SDs) above the mean for age.
- if levels are at + 3 SDs or higher, GH dose should be lowered.
- if between + 2 and + 3 SDs, use clinical judgment to decide on dosage.

Weak recommendation based on very low-quality evidence.<sup>9</sup> However, details of the supporting evidence were unclear from the publication.

### ***Safety of GH Treatment***

The guideline did not include any specific formal recommendation statements regarding the adverse effects of GH therapy. Authors provided the following notes on the safety of treatment. They were supported by evidence as indicated in parentheses.

- Children with TS have a higher risk of intracranial hypertension and slipped capital femoral epiphysis compared to patients with other growth disorders on GH treatment (1 observational study, data were not reported). Development or progression of scoliosis was "more common" in children with TS who are on GH therapy. (1 observational study, data not reported). These adverse events may be due to rapid increase in linear growth because of GH therapy.
- Children with TS treated with GH may be at a higher risk for pancreatitis than those treated with GH for other growth disorders. (1 study, data not reported).
- Even after discontinuation of GH therapy, there may be continued low insulin sensitivity. However, children with TS receiving GH were found to have reduced abdominal adiposity, and 'significantly

better' glucose tolerance than patients not treated with GH (data not reported). Therefore, the beneficial effects of GH on body composition and regional fat deposition may outweigh the effects on insulin sensitivity.

- Evidence on whether GH treatment increases the risk of type 2 DM in people with TS is mixed. (3 studies, data were not reported).
- "Reassuring" evidence from long-term studies on outcomes such as blood pressure and cardiovascular disease risk (4 studies), carbohydrate and lipid metabolism (4 studies), body composition (2 studies), bone mineralization (1 study), body proportions (2 studies), and otitis media and hearing loss (1 study). Data not reported. However, the authors flagged that the trials may not be adequately powered for the safety outcomes and that the findings should be interpreted cautiously.

### ***Concomitant Treatment***

Concurrent treatment with oxandrolone is suggested by guideline authors:

- when the patient is 10 years or older
- at a starting dose of 0.03 mg/kg/ day
- at a maintenance dose below 0.05 mg/kg/ day
- if adult height will likely be unsatisfactory with a GH only treatment
- if TS was diagnosed late, and GH treatment was therefore also delayed.

Weak recommendation based on strong evidence.<sup>9</sup> Supporting evidence showed that, compared to children who received GH only treatment, those who received concomitant treatment with GH and oxandrolone were 2 to 5 cm taller as adults (evidence from GRADE evaluation of 3 studies). Evidence from 6 studies suggests that concurrent treatment with oxandrolone is associated with a modest synergistic increase in growth (data not reported). Possible adverse effects are delayed breast development and dose-dependent virilization (e.g., clitoromegaly, hirsutism, acne, voice deepening). The main limitation of evidence as noted by the authors, was a high between-study heterogeneity. Therefore, a meta-analysis was not conducted.

This guideline<sup>9</sup> also recommends against adding very-low-dose estrogen supplementation in the prepubertal years to further promote growth (Weak recommendation based on low-quality evidence<sup>9</sup>). One study found that concurrent treatment with GH and very-low-dose estrogen was associated with a modest synergistic increase in adult height, cognition, and normal timing of thelarche. However, due to the lack of any other evidence, the lack of long-term safety information, and the absence of optimized dosing strategy, the authors do not recommend concurrent treatment.

### ***Health Surveillance for Comorbidities Throughout the Lifespan***

The guideline recommends regular clinical evaluation for scoliosis every 6 months while receiving GH therapy, and then annually until growth is completed (strong recommendation based on very low quality evidence).<sup>9</sup>

It also recommends coordinating GH therapy with orthopedic care if spine abnormalities are detected at the beginning or during treatment (strong recommendation based on very low quality evidence).<sup>9</sup>

The authors provided the following notes on the bone-related effects of GH therapy. They were supported by evidence as indicated in parentheses.

- GH therapy may increase hand and foot size (1 study).
- It may increase bone size but is not associated with not with changes to bone mineral density or increased fracture risk (1 study).
- GH therapy could increase the longitudinal axis and anterior rotation of the mandible, but the pre-existing retrognathia persists (2 studies).
- GH therapy will not result in acromegaloid craniofacial features in people with TS (3 studies).

## Limitations

We identified 1 evidence-based guideline<sup>9</sup> regarding the use of GH (somatropin) for TS. In previous sections, we have summarized the strengths and limitations of this guideline. The main limitation was that several recommendations were formulated through consensus from expert opinion of the working group based on limited available evidence. However, it was unclear whether the authors systematically searched for evidence (and found limited evidence) supporting them. Therefore, these recommendations should be interpreted with caution.

In Canada, somatropin products are approved for children with TS in whom the epiphyses are not closed.<sup>7</sup> We did not identify any recommendations that specifically addressed treatment eligibility in relation to epiphyseal closure. We did not identify any recommendations related to outcomes such as laboratory cut-offs for treatment eligibility or for treatment discontinuation (e.g., criteria for discontinuation due to lack of treatment effect). The recommendations in the guideline were produced during a meeting in 2016; it is possible that new studies regarding the use of GH for children with TS have been published since. Therefore, the recommendations provided in the guideline may not reflect the current evidence landscape. Lastly, we did not identify any guidelines published in Canada regarding GH therapy for children and adolescents with TS. The applicability of the included guideline in Canadian settings is unclear.

## Conclusions and Implications for Decision- or Policy-Making

We included 1 guideline from the 2016 Cincinnati International Turner Syndrome Meeting,<sup>9</sup> that provided recommendations regarding GH therapy in children with TS. The guideline was developed for US and European countries. Recommendations were formulated either based on evidence found from systematic literature searches or from expert opinion and consensus. We also identified a perspective document from the GRS (2019),<sup>11</sup> that discussed evaluation and treatment of short stature due to various causes in children. This publication was excluded because it was not an evidence-based guideline. The characteristics and relevant recommendations from this publication are summarized in [Appendix 5](#).

The included guideline<sup>9</sup> strongly recommends early initiation of GH treatment (around 4 to 6 years of age) if the child with TS has evidence of growth failure. Recommended dose of GH is 40 mcg/kg/day to 50 mcg/kg/

day and can be increased if adult height potential is considerably low (strong recommendation). GH therapy should be monitored by regular height measurement (strong recommendation) and monitoring of IGF-I levels (weak recommendation) to regulate dosage. Authors noted that GH therapy could be discontinued when a bone age greater than 14 years is attained, and when the height is not increasing by at least 2 cm per year. The authors noted that there is no physiological reason to continue GH therapy after puberty is completed. However, no specific recommendations were made regarding epiphyseal plate closure and treatment discontinuation. If oxandrolone is given concurrently, patients should be 10 or older. Concomitant treatment of GH with low-dose estrogen for growth promotion is not recommended. Lastly, children with TS receiving GH therapy should be evaluated regularly for scoliosis. While no recommendations specific to the safety of GH were made, authors noted that there is an increased risk of adverse events such as intracranial hypertension, slipped capital femoral epiphysis, scoliosis, and pancreatitis in children with TS compared to those receiving GH for other growth disorders. However, these statements should be interpreted cautiously since the supporting evidence is scant. The guideline was relatively well conducted, with the main limitation of basing several recommendations on expert opinion and consensus.

The GRS perspective document<sup>11</sup> recommended starting GH therapy with a dose at the higher end of the range if TS was diagnosed late and noted that higher IGF-I levels (i.e., more than 2 SDs above the mean for age) may be needed for effective growth in some patients. These statements should be interpreted with caution as the supporting evidence was unclear. We did not conduct a critical appraisal of the publication.

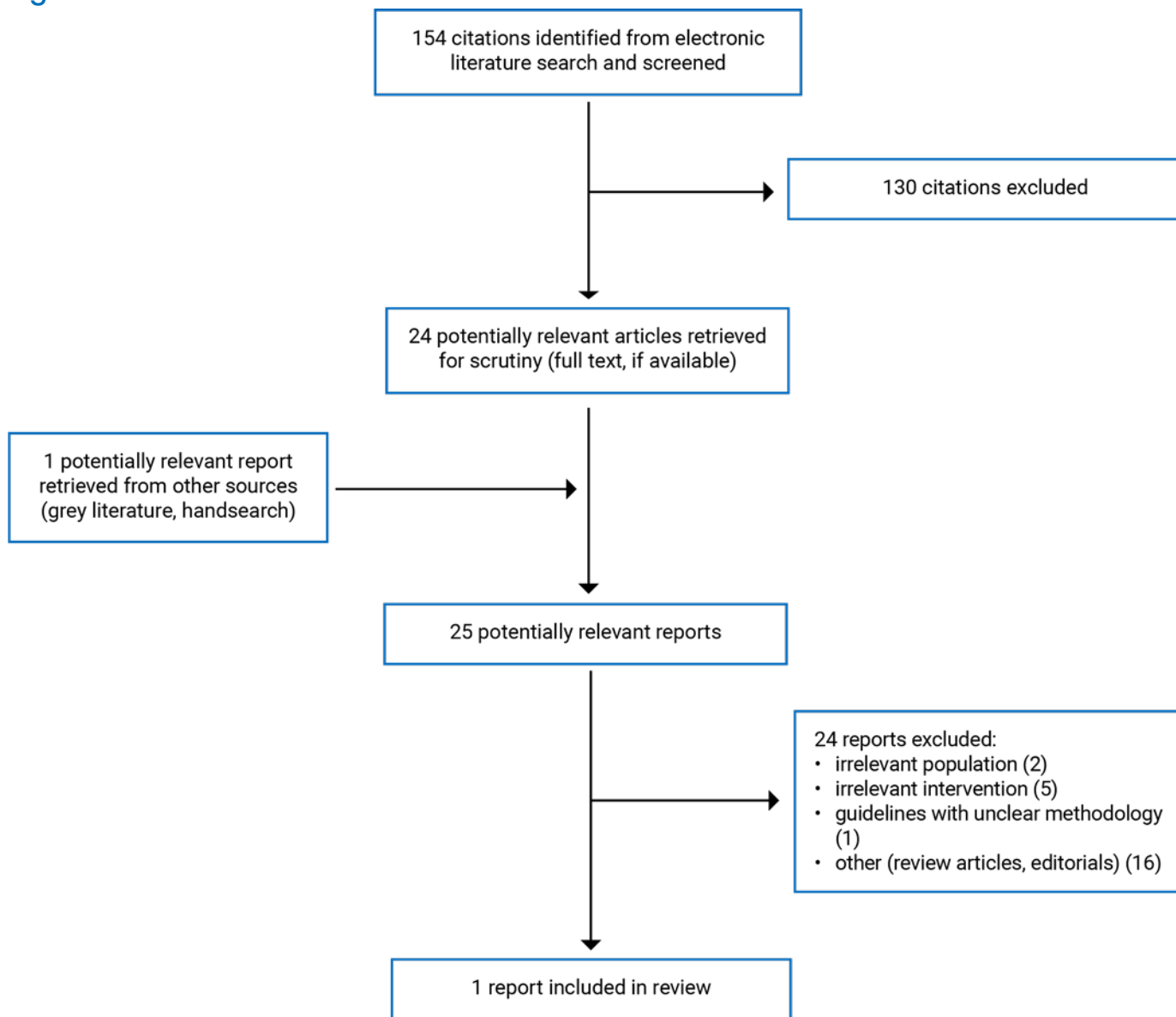
Growth promotion is 1 of the main objectives in the care for children with TS.<sup>4</sup> Guidelines help clinicians and other health care providers make evidence-based decisions in clinical care. The recommendations from the included guideline to initiate early GH therapy in children with TS, providing recommended dosage, as well as recommendations about concurrent treatment with oxandrolone, could inform policy decisions. However, the recommendations should be implemented in light of their limitations. For many of the recommendations from the included guideline,<sup>9</sup> such as those related to recommendations about health surveillance for orthopedic comorbidities, and treatment monitoring, the supporting evidence was unclear from the publication. They did not make recommendations regarding treatment eligibility in relation to epiphyseal closure, or regarding IGF-I thresholds for treatment discontinuation. The guideline included in this report was published in 2017.<sup>9</sup> Several studies have since been published evaluating long-term effectiveness and safety of GH therapy in children with TS.<sup>4</sup> [Appendix 6](#) presents some of the comparative and real-world studies published in the recent years. A detailed review of the newer studies is beyond the scope of this report; however, the evidence appears to be mostly consistent with the supporting evidence from the guideline. Future guidelines could focus on evidence regarding treatment eligibility in relation to epiphyseal closure, treatment duration, and criteria for discontinuation of treatment to inform precise recommendations on these aspects of GH therapy in children with TS.

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## Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies





## Appendix 2: Characteristics of Included Publications

**Table 2: Characteristics of Included Guideline From the 2016 Cincinnati International Turner Syndrome Meeting, Gravholt et al.(2017)<sup>9</sup>**

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
<p>Intended users: Health care providers (primary care providers and specialists)</p> <p>Target population: Patients with TS</p>	<p>Diagnostics, growth interventions, fertility related interventions, cardiovascular interventions, transition from pediatric to adult care, general health surveillance</p> <p>Relevant intervention: Growth hormone therapy</p>	<p>Relevant outcomes: Height, quality of life, mortality. Cardiovascular side effects, and masculinization.</p>	<p>Evidence collected through systematic literature search. 24 publications were included of which 12 were about growth hormone therapy.</p>	<p>Conducted using GRADE framework. Evidence was ranked as very low, low, moderate, or strong.</p>	<p>Recommendations were formulated based on quality of evidence, risk-benefit balance, patient preferences and values, as well as resource and implementation considerations. Recommendations are graded as strong (worded as recommend) or weak (worded as suggest). Some other recommendations proposed by committee members (and were not evidence supported) were also included.</p>	<p>Recommendations were finalized during 2 working group meetings. Consensus arrived through discussion. Patient partner was involved in the working-groups. Draft guidelines were reviewed by professional societies and revised accordingly.</p>

GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; TS = Turner syndrome.

Note this appendix has not been copy-edited.

## Appendix 3: Critical Appraisal of Included Publications

Note this appendix has not been copy-edited.

**Table 3: Strengths and Limitations of the Guideline From the 2016 Cincinnati International Turner Syndrome Meeting, Gravholt et al.(2017)<sup>9</sup> Using AGREE II<sup>8</sup>**

Item	Gravholt et al. (2017) <sup>9</sup>
<b>Domain 1: Scope and purpose</b>	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
<b>Domain 2: Stakeholder involvement</b>	
4. The guideline development group includes individuals from all relevant professional groups.	Partially, most of the working group members were clinicians.
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes, patient advocacy group members present for the working group meetings
6. The target users of the guideline are clearly defined.	Yes
<b>Domain 3: Rigour of development</b>	
7. Systematic methods were used to search for evidence.	Partially, for some of the recommendations
8. The criteria for selecting the evidence are clearly described.	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Partially, for some of the recommendations
13. The guideline has been externally reviewed by experts before its publication.	Yes
14. A procedure for updating the guideline is provided.	No
<b>Domain 4: Clarity of presentation</b>	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
<b>Domain 5: Applicability</b>	
18. The guideline describes facilitators and barriers to its application.	Yes

Item	Gravholt et al. (2017) <sup>9</sup>
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	No
<b>Domain 6: Editorial independence</b>	
22. The views of the funding body have not influenced the content of the guideline.	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II.

## Appendix 4: Main Study Findings

**Table 4: Summary of Recommendations of the Guideline From the 2016 Cincinnati International Turner Syndrome Meeting, Gravholt et al. (2017)<sup>9</sup>**

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
<b>Initiation of GH therapy</b>	
<p><b>Recommendation statement:</b>            “We recommend initiating growth hormone (GH) treatment early (around 4–6 years of age, and preferably before 12–13 years) in the following circumstances: the child already has evidence of growth failure (e.g., below 50th percentile height velocity (HV) observed over 6 months in the absence of other treatable cause of poor growth), the child is already short or has a strong likelihood of short stature (e.g., short parents and short predicted adult height or already pubertal at the time of diagnosis)<sup>9</sup> (p.G2)</p> <p><b>Supporting evidence:</b>            This recommendation was informed by evidence from 14 RCTs (of which 4 were included in a Cochrane SR) published from 1991 to 2011. A GRADE evaluation of these 14 studies were conducted.</p> <ul style="list-style-type: none"> <li>• A height gain of 1cm per year of GH treatment can be expected (10 studies)</li> <li>• High GH doses at ‘young ages’ could result in gains in height as much as 15 to 17 cm than their projected adult height without GH (2 studies)</li> <li>• Compared to no treatment or placebo, GH-treated groups had higher growth rates. (4 studies).</li> <li>• Patients treated with GH were taller as adults compared to those not treated with GH, with differences ranging from 0.5 to 1.5 SDs.(3 studies)</li> <li>• Authors noted the main limitations of the evidence as heterogeneity, lack of adequate blinding, high loss to follow-up in the long-term studies, and unclear definitions of primary end points across the studies.</li> </ul> <p><b>Authors’ comments:</b></p> <ul style="list-style-type: none"> <li>• If patients were able to catch-up growth to normal range within the first 2 years of treatment, their height velocity (rate of increase of height) was closer to normal for age, and they may acquire adult height within the lower normal range.</li> <li>• Since patients with TS lack the pubertal growth spurt due to lower endogenous GH and estrogen, during puberty GH-treated patients may fall behind their peers without TS. However, compared to patients with TS, their height should continue to increase.</li> <li>• A younger age at treatment initiation, with at least 4 years of GH therapy before puberty, is associated with greater treatment effects. (Evidence from 10+ studies)</li> </ul>	<p>Strong recommendation based on moderate quality evidence.</p>

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
<ul style="list-style-type: none"> <li>Parental heights and heights at treatment initiation are nonmodifiable factors affecting adult height.</li> <li>Therapy can be continued until the patient reaches desired height or when there is no more growth potential remaining. This is characterized by bone age &gt; 14 years, and height velocity of &lt; 2cm per year.</li> <li>There is no physiological justification to continue GH treatment after completing puberty.</li> </ul>	
<b>Dose and frequency of GH treatment</b>	
<p><b>Recommendation statement:</b>            “We recommend using a GH dose of 45–50 µg/kg/day or 1.3–1.5 mg/m<sup>2</sup>/day (4.0–4.5 IU/m<sup>2</sup>/day) in most instances, increasing to 68 µg/kg/day (2.0 mg/m<sup>2</sup>/day) if adult height potential is substantially compromised”<sup>9</sup> (p.G2)</p> <p><b>Supporting evidence:</b> NR</p> <p><b>Authors’ comments:</b></p> <ul style="list-style-type: none"> <li>Starting doses in North America: 0.350 to 0.375 mg /kg/week (50 to 54 mcg/kg/day), administered in divided doses 7 days a week.</li> <li>Starting doses in Europe: 1.3 to 1.4 mg/m<sup>2</sup>/day (4.0 to 4.3 IU/m<sup>2</sup>/day), in divided doses 7 days a week.</li> <li>Starting doses in Australasia: 0.6 to 1.4 mg/m<sup>2</sup>/day (4.5 to 9.5 mg/m<sup>2</sup>/week), in divided doses 7 days a week</li> <li>Higher doses are only needed in patients with very poor height prognosis, within the approved dose range.</li> <li>Potential risks and benefits should be discussed before administering increased doses.</li> </ul>	Strong recommendation based on strong evidence.
<b>Treatment monitoring</b>	
<p><b>Recommendation statement:</b>            “We recommend monitoring growth-promoting treatment by measurement of height at least every 4–6 months during the first year of treatment and at least every 6 months thereafter.”<sup>9</sup> (p.G2)</p>	Strong recommendation based on moderate quality evidence.
<p><b>Recommendation statement:</b>            “We recommend monitoring the safety of growth-promoting therapy by measurement of IGF-I at least annually.”<sup>9</sup> (p.G2)</p>	Strong recommendation based on low-quality evidence.
<p><b>Recommendation statement:</b>            “We suggest that for TS patients treated with GH the measured IGF-I should ideally be no greater than 2 SDS above the mean for age. If an IGF-I value is measured above +3 SDS, a GH dose decrease is warranted. For an IGF-I value between +2 SDS and +3 SDS, clinical judgment should guide further GH dose selection.”<sup>9</sup> (p.G2)</p> <p><b>Supporting evidence:</b> NR</p>	Weak recommendation based on very low-quality evidence.

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
<b>Safety of GH treatment</b>	
<p><b>Authors' notes:</b></p> <ul style="list-style-type: none"> <li>• Children with TS on GH therapy has been found to have a “higher risk” of intracranial hypertension and slipped capital femoral epiphysis compared to patients with ISS or GHD on GH treatment. (1 observational study, data NR).</li> <li>• Compared to other growth disorders, development or progression of scoliosis was “more common” in people with TS. (1 observational study, data NR)</li> <li>• Authors noted that these adverse events may be due to rapid increase in linear growth because of GH therapy.</li> <li>• Patients with TS may be “at greater risk” for pancreatitis than children treated with GH for other growth disorders. (1 study, data NR)</li> <li>• Patients with TS are at higher risk of diseases associated with carbohydrate metabolism. Evidence from long-term studies suggest that there is no increased risk with GH treatment.(7 studies).</li> <li>• There may be continued low insulin sensitivity even after discontinuation of GH (1 study). But GH-treated patients with TS were found to have reduced abdominal adiposity, and ‘significantly better’ glucose tolerance than patients not treated with GH. (1 study). Therefore, the beneficial effects of GH on body composition and regional fat deposition may outweigh the effects on insulin sensitivity.</li> <li>• Mixed evidence on whether GH treatment increase the risk of type 2 DM in patients with TS.</li> <li>• The evidence from long-term clinical studies has been “reassuring” in terms of safety of GH treatment on outcomes such as blood pressure and cardiovascular disease risk (4 studies), carbohydrate and lipid metabolism (4 studies), body composition (2 studies), bone mineralization (1 study), body proportions (2 studies), and the otitis media and hearing loss (1 study). However, the authors flag that the trials may not be adequately powered for the safety outcomes and that the findings should be interpreted with caution.</li> </ul>	—
<b>Concomitant treatment</b>	
<p><b>Recommendation statement:</b></p> <p>“We suggest concomitant treatment with oxandrolone from the age of 10 years or older at 0.03 mg/kg/day and maintained below 0.05 mg/kg/day, if the diagnosis of TS (and therefore GH treatment initiation) is delayed, and/or adult height outcome is likely to be unsatisfactory with the standard GH dose alone.”<sup>99</sup> (p.G2)</p> <p><b>Supporting evidence:</b></p> <ul style="list-style-type: none"> <li>• Adding oxandrolone to GH treatment is associated with “modest synergistic increase” in growth response. (6 studies)</li> <li>• Adult height was around 2 to 5 cm higher in patients who received concomitant treatment with oxandrolone</li> </ul>	Weak recommendation based on strong evidence.

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
<p>compared to those who received GH only (from GRADE evaluation of 3 studies)</p> <ul style="list-style-type: none"> <li>• There may be adverse effects such as delayed breast development, dose-dependent virilization (e.g., clitoromegaly, hirsutism, acne, voice deepening).</li> <li>• Authors noted that there was high between-study heterogeneity. Therefore, a meta-analysis was not conducted.</li> </ul> <p><b>Authors' comments:</b></p> <ul style="list-style-type: none"> <li>• Oxandrolone should not be added to the treatment until the patient is around 10 years old, starting dose of 0.03mg/kg/day and maximum maintenance dose 0.05mg/kg/day.</li> </ul>	
<p><b>Recommendation statement:</b></p> <p>"We suggest to not routinely add very low-dose estrogen supplementation in the prepubertal years to further promote growth."<sup>9</sup> (p.G2)</p> <p><b>Supporting evidence:</b></p> <ul style="list-style-type: none"> <li>• Concomitant treatment of GH and very low dose estrogen, there was "modest synergistic increase" in adult height, modest improvements in cognition and memory, and normal timing of thelarche (1 study).</li> <li>• However, authors highlighted the limitations such as no other evidence, lack of optimized dosing strategy, and lack of evidence regarding long-term safety.</li> <li>• Therefore, adding low-dose estrogen as a growth-promoting therapy is not recommended.</li> </ul>	<p>Weak recommendation based on low-quality evidence.</p>
<b>Health surveillance for comorbidities throughout the lifespan</b>	
<p><b>Recommendation statement:</b></p> <p>"We recommend clinical evaluation for scoliosis every 6 months during GH therapy or otherwise annually until growth is completed."<sup>9</sup> (p.G5)</p>	<p>Strong recommendation based on very low quality evidence.</p>
<p><b>Recommendation statement:</b></p> <p>"We suggest treatment with GH be coordinated with orthopedic care if spine abnormalities are present at the start of therapy or if they develop during therapy."<sup>9</sup> (p.G5)</p> <p><b>Supporting evidence and authors' notes:</b></p> <ul style="list-style-type: none"> <li>• GH Therapy may:           <ul style="list-style-type: none"> <li>◦ Increase hand and foot size (1 study)</li> <li>◦ Increase bone size but is not associated with not with changes to bone mineral density or increased fracture risk (1 study).</li> <li>◦ Increase the longitudinal axis and anterior rotation of the mandible, but the pre-existing retrognathia persists (2 studies.)</li> </ul> </li> </ul>	<p>Weak recommendation based on very low quality evidence.</p>

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
<ul style="list-style-type: none"> <li>• GH therapy will not cause acromegaloid craniofacial features in patients with TS (3 studies)</li> <li>• Scoliosis may develop or progress with GH therapy.</li> </ul>	

DM = diabetes mellitus; GH = growth hormone; GHD = growth hormone deficiency; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; IGF -1 = insulin-like growth factor-1; ISS = idiopathic short stature; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; TS = Turner syndrome.

Note this appendix has not been copy-edited.



## Appendix 5: Other Relevant Guidelines

Note that this appendix has not been copy-edited.

**Table 5: Characteristics of Other Guideline (GRS Perspective, 2019)<sup>11</sup>**

Study design and methodology	Intended users, target population	Intervention and practice considered	Evidence collection, selection, and synthesis	Recommendations development and evaluation
Expert Opinion from a workshop. Report from a 3-day workshop organized by the GRS. The participants included endocrinologists, basic scientists, representatives from pharmaceutical companies and from regulatory agencies (e.g., EMA, FDA)	Intended users: Health care providers. Target population: Children with short stature. Relevant population: Children with TS	Diagnosis and treatment of short stature in children. Relevant intervention: GH treatment in children with TS	No systematic evidence search conducted. Quality of evidence not assessed	Recommendations were developed by workshop attendees through consensus or voting. Draft report reviewed by the attendees. Strength of recommendations or supporting evidence not reported.

EMA = European Medicines Agency; GH = growth hormone; GRS = Growth Hormone Research Society; TS = Turner syndrome.

### Guidelines and Recommendations with Alternative Methodology

Collett-Solberg PF, Ambler G, Backeljauw PF, et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. *Horm Res Paediatr*. 2019;92(1):1 to 14.

#### Description

This publication was a report from the workshop conducted by Growth Hormone Research Society International to discuss the evaluation and treatment of short stature in children. It provides recommendations based on expert opinion regarding GH treatment in children with TS. Since the recommendations provided were not evidence-based, this publication was excluded from the main report. The characteristics of the publication are summarized in [Table 5](#).

#### Relevant Recommendations

For indications other than growth hormone deficiency the authors suggested a higher dose than for GHD. They recommend starting GH at approved dose ranges, and to use prediction models to optimize the dosage.

In case of late diagnosis of TS, the authors recommend starting rhGH on a dose at the higher end of the approved range. (Specific doses NR).

IGF monitoring: In some children with TS, IGF-I levels + 2SD is maybe needed for effective growth.

## Appendix 6: References of Potential Interest

### Systematic Reviews

Mohamed S, Alkofide H, Adi YA, Amer YS, AlFaleh K. Oxandrolone for growth hormone-treated girls aged up to 18 years with turner syndrome. *Cochrane Database Syst Rev*. 2019; 2019(10):CD010736. [PubMed](#)

### Non-Randomized Studies

Cleemann Wang A, Hagen CP, Nedaeifard L, Juul A, Beck Jensen R. Growth and Adult Height in Girls With Turner Syndrome Following IGF-1 Titrated Growth Hormone Treatment. *J Clin Endocrinol Metab*. 2020;105(8):2566–2574. [PubMed](#)

Backeljauw P, Blair JC, Ferran JM, et al. Early GH Treatment is Effective and Well Tolerated in Children with Turner Syndrome: NordiNet@ IOS and ANSWER Program [published online ahead of print, 2023 Mar 22]. *J Clin Endocrinol Metab*. 2023;dgad159. [PubMed](#)

Quigley CA, Fechner PY, Geffner ME, et al. Prevention of Growth Failure in Turner Syndrome: Long-Term Results of Early Growth Hormone Treatment in the “Toddler Turner” Cohort. *Horm Res Paediatr*. 2021;94(1-2):18-35. [PubMed](#)

Ross J, Fridman M, Kelepouris N, et al. Factors Associated With Response to Growth Hormone in Pediatric Growth Disorders: Results of a 5-year Registry Analysis. *J Endocr Soc*. 2023;7(5):bvad026. [PubMed](#)

### Review Articles

Al Herbish AS, Almutair A, Bin Abbas B, et al. Diagnosis and management of growth disorders in Gulf Cooperation Council (GCC) countries: Current procedures and key recommendations for best practice. *Int J Pediatr Adolesc Med*. 2016;3(3):91-102. [PubMed](#)

### Additional References

Hoag BD, Tsai SL, Williams DD, Cernich JT. International Guideline Adherence in Girls with Turner Syndrome: Multiple Subspecialty Clinics Versus Coordinated Multidisciplinary Clinic. *Endocr Pract*. 2022;28(12):1203-1209. [PubMed](#)

Navarro R, Dunn JD, Lee PA, Owens GM, Rapaport R. Translating clinical guidelines into practice: the effective and appropriate use of human growth hormone. *Am J Manag Care*. 2013;19(15 Suppl):s281-s289. [PubMed](#)

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