

**TEXAS CHILDREN'S HOSPITAL**  
**EVIDENCE-BASED OUTCOMES CENTER**  
**Puberty Induction in Girls with Turner Syndrome**  
**Evidence-Based Practice Course Evidence Summary**

**Inclusion Criteria**

- Girls with Turner Syndrome

**Critically Analyze the Evidence**

The **GRADE criteria** were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

Recommendation	
<b>STRONG</b>	Desirable effects clearly outweigh undesirable effects or vice versa
<b>WEAK</b>	Desirable effects closely balanced with undesirable effects
Quality	Type of Evidence
<b>High</b>	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
<b>Moderate</b>	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
<b>Low</b>	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
<b>Very Low</b>	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

**PICO Question 1:** In girls with Turner Syndrome, what is the best early marker of gonadal failure?

**Recommendation(s):**

Weak recommendation with very low quality evidence to utilize antimüllerian hormone (AMH) and inhibin B as early markers of ovarian failure. <sup>(1-10)</sup>

Weak recommendation with very low quality evidence to NOT use FSH as an early marker of ovarian failure. <sup>(1-10)</sup>

Up to 20-30% of affected girls have spontaneous pubertal development and 2-5% have spontaneous menarche. <sup>(1)</sup> FSH, inhibin B, and AMH have been proposed as early biochemical markers to identify Turner Syndrome (TS) girls who will benefit of puberty induction rather than waiting until 14 years of age to assess clinically if puberty has occurred.

**Inhibin B:** In healthy girls, inhibin B expresses a biphasic pattern with high levels during infancy, low levels during prepubertal years, with a subsequent rise at initiation of puberty. <sup>(2)</sup> In adult women, inhibin B levels reflect the number of follicles present. <sup>(3)</sup> Gravholt found that all TS girls had undetectable inhibin B levels, while *most* prepubertal controls had detectable levels. <sup>(4)</sup> Hagen found that 95% of the TS girls with undetectable inhibin B levels had no spontaneous puberty and the only girl who had signs of puberty and an undetectable level had pubertal arrest. <sup>(5)</sup>

**AMH:** In normal girls, AMH has a biphasic pattern, with a rise during infancy, followed by a nadir between 1 and 4 years of age, followed by a rise between 4 and 8 years of age. <sup>(2)</sup> In adult women, AMH levels correlate with the primordial follicle count and is considered a marker of ovarian aging. <sup>(6)</sup> Hagen showed that there is a strong correlation between the karyotype and AMH levels, with higher levels on 45,X/46,XX girls (who also have highest rates of ovarian function); followed by miscellaneous karyotypes, and lastly monosomic girls (who have the lowest rates of puberty). In addition, TS girls with absent spontaneous puberty had the lowest levels, undetectable in 75% of them. He calculated that a cutoff value of <8 pmol/L had 96% sensitivity for POF. However, his data analyzes the values of girls 12 to 25 years old rather than younger. <sup>(2)</sup> Visser and Lunding also had promising results: AMH was undetectable in most girls with absent spontaneous puberty and detectable in most girls with spontaneous puberty. Visser calculated OR of spontaneous breast development and menarche of 19.3 and 47.6, respectively, with detectable AMH levels <sup>(7)</sup>; and Lunding calculated a sensitivity of 95% for premature ovarian failure when AMH levels were <3. Unfortunately, in Lunding's data, 30% of girls without spontaneous puberty still had detectable AMH levels. <sup>(8)</sup> The combination of AMH and inhibin B was evaluated by Hagen, who found that 1/1 of the patients who had ovarian function and an AMH level below his cutoff point, inhibin B was detectable. <sup>(2)</sup>

**FSH:** TS girls have a biphasic FSH pattern: levels are increased during the first 2 years of life, decline gradually during childhood, and rise again at the usual age for puberty. Between the 5<sup>th</sup> and 10<sup>th</sup> year of life, gonadotropin levels are low, usually indistinguishable from normal girls. <sup>(9,10)</sup> When using ultrasensitive assays, all studies showed that TS girls have mean higher FSH levels at all ages. <sup>(4,5,9)</sup> Gravholt's showed that at after the age of 10, none of the prepubertal controls had FSH levels above 9.0 and all of the TS girls after the age of 10 had FSH levels >7.7 U/L. <sup>(4)</sup> However, Chrysis's and Hagen's data show overlap with prepubertal girls and TS. <sup>(5,9)</sup>

In summary, low or undetectable levels of AMH and inhibin B may be useful early markers of ovarian failure; however, more studies are needed to establish: 1) a cutoff value for each test in the 10-12 years TS population; 2) sensitivity, specificity, and negative and positive predictive values of each marker and their combination for spontaneous pubertal development. On the contrary, despite the fact that TS girls have higher FSH levels than controls, FSH is not a useful marker as during childhood, the difference is not significant. FSH is rather a late marker of ovarian failure as it rises *after* central puberty onset and lack of negative feedback from dysgenetic ovaries.

**PICO Question 2:** In girls with Turner Syndrome, what is the best age to start sex hormone replacement?

**Recommendation(s):**

Strong recommendation with low quality evidence to start estrogen close to the age of 12 years to maximize growth, as long as height prediction is adequate. <sup>(10-40)</sup>

Weak recommendation with very low quality evidence to consider delaying puberty induction to the age of 14 years in patients with severe short stature. <sup>(10-40)</sup>

**Remarks:**

With the approach of starting estrogen close to the age of 12 years, there is low quality evidence that the development of secondary sexual characteristics occurs on average 2 years later than their peers and very low quality evidence of better bone mineral density acquisition.

In delaying puberty induction to the age of 14 years, the improved height is at the expense of irreversible decrease in BMD accrual (very low quality evidence) and non-peer matched development of secondary sexual characteristics (low quality evidence).

There are three approaches in regards to starting estrogen: late (>14-16 years of age), early (12-13 years of age) and prepubertal (5-8 years of age), with late being the classic approach to achieve better height outcomes before the almost universal use of growth hormone in this population. However, this approach overlooks the importance of timing of secondary sexual characteristics or bone mineral density acquisition. The age of puberty induction should take into consideration at least three outcomes: height, age of attainment of secondary sexual characteristics, and bone mineral density.

**Secondary sexual characteristics:** Optimal timing of puberty induction should allow the girl to experience the physical changes of puberty at the same time as her peers. In the U.S., 50% of girls have undergone thelarche by the age of 10.2 years and 95% by the age of 12.1 years, with menarche occurring  $2.3 \pm 1.0$  years later. <sup>(11)</sup> In girls with TS, when puberty induction is started at ~12 years, thelarche occurs at 12.6-12.9 years of age <sup>(12-17)</sup> and menarche at 14.5 to 15 years of age. However, in the RCT of ultra-low dose estrogen before the age of 12 years, thelarche occurred at 11.1 years, which is closer to the mean of the population. <sup>(15)</sup> Although it is only one small study, it raises the question of a potential benefit of prepubertal ultra-low dose of estrogen to allow a more age-appropriate thelarche.

**Uterine development:** Different studies have shown that young adult TS women have hypoplastic uteruses with pre-pubertal configurations. <sup>(18,19)</sup> Appropriate dose and timing of estrogen should induce normal uterine development. <sup>(20)</sup> It was not possible to evaluate the effect of age of puberty induction in uterine size, as none of the studies separated the patients by age of puberty induction. The majority of studies showed that TS girls had uterine sizes smaller than controls <sup>(16,21-23)</sup>; however, these differences tended to disappear after 3 and 5 years of HRT. <sup>(23,24)</sup> Finally, the importance of uterine outcomes to evaluate pubertal regimens is controversial since pregnancies remains particularly challenging even with donor eggs, due to the high prevalence of maternal cardiovascular complications. <sup>(18,20)</sup>

**Height:** Short stature is a common feature of TS. Growth failure is exacerbated with the absence of a pubertal growth spurt. <sup>(18,25,26)</sup> Multiple factors affect the final height, including GH and estrogen treatment. <sup>(10,18)</sup> Estrogen has a biphasic effect on growth: at lower doses, estrogen stimulates growth and at higher levels, it inhibits growth. <sup>(27)</sup> There is evidence that late induction of puberty results in higher final heights (0.3 cm per year delayed); however, this difference is minimal and likely not clinically significant when GH is used, which is the current standard of care. Furthermore, if puberty is delayed, the pubertal spurt is hampered. <sup>(28)</sup> The 2 RCTs that compared ultra-low doses of estrogen before the age of 12 years showed conflicting results, none of them statistically significant. An explanation for this difference could be that Rosenfield (+ benefit) used parenteral estrogen, which results in higher levels of IGF-1 compared to oral estrogen.

**Bone mineral density:** Patients with TS have higher fracture rates and lower cortical and trabecular BMD, during early childhood, adolescence, and adulthood. Cortical BMD seems to be independent of pubertal and hormonal status, while trabecular bone density is associated with hormonal status. <sup>(29-31)</sup> Data extrapolated from the normal population show that peak bone mass accrual occurs early in adolescence (11-12 years of age). <sup>(32)</sup>

Given this, we would anticipate that early use of estrogen should be associated with improved BMD in TS. Small observational studies have shown that there is no benefit for BMD accrual of starting estrogen at an age younger than 12 years; however, if puberty is induced after the age of 14 years, BMD is significantly less. It is controversial as to whether patients who start late eventually develop BMD similar to the ones of early start, as one study showed <sup>(33)</sup> it and the other didn't. <sup>(23)</sup> Studies evaluating BMD have multiple flaws: no RCTs; different estrogen doses, route of delivery; different methods to assess BMD and adjust by height, age, and pubertal status; and different lengths of follow-up.

**PICO Question 3:** In girls with Turner Syndrome, is enteral vs. transdermal the best route to deliver estrogen for puberty induction?

**Recommendation(s):** Weak recommendation with very low quality evidence to prefer transdermal vs. oral estrogen for puberty induction. <sup>(41-50)</sup>

Estradiol is normally secreted into the systemic circulation exposing all tissues to similar concentrations. This effect is mimicked by parenteral or transdermal administration. In contrast, oral estrogens undergoes hepatic first pass metabolism; therefore, the liver is exposed to a greater dose of estrogen. Studies in postmenopausal women have shown differences in lipids, insulin sensitivity, blood pressure, growth hormone levels and factors, and risk for thromboembolism in patients with oral vs. transdermal estrogen; however, the clinical significance in young TS girls is unclear. <sup>(41)</sup> There are multiple limitations when assessing these studies: different doses/protocols, different compounds, different populations (pre- vs. postpubertal), small sample sizes, and different outcomes.

**Secondary sexual characteristics:** In the 4 observational studies evaluated, TD therapy seems to provide TS girls with more rapid breast tissue development compared to oral therapy, while still being at a normal physiologic tempo. Girls on TD therapy also had higher rates of menarche during the first year, likely reflecting uterine development.

**Uterine development:** Two small studies describe outcomes when using transdermal estrogen. <sup>(42,43)</sup> Piipo describes an adequate increase in uterine length and size after 5 years of TD therapy. Nabhan describes more marked increase in length and volume in patients using TD vs. oral estrogen, suggesting a benefit of TD estrogen.

**Height and growth:** Three randomized block studies (treatment blocks ranging from 2 to 6 weeks) <sup>(44-46)</sup> and 2 RCTs of 12 months duration each <sup>(42,47)</sup> showed no significant difference in IGF-1 levels between girls receiving TD vs. oral estrogen. Clinically, there is 1 RCT comparing growth in girls treated with TD vs. oral estrogen, which showed no difference in growth velocity. <sup>(42)</sup> However, in a more recent small descriptive retrospective study, Cakir showed that patients induced with TD estrogen had higher growth velocities and higher chronological to bone age difference suggestive of slower bone age advancement. <sup>(48)</sup>

**Bone mineral density:** Three studies evaluated BMD in TS patients receiving TD estrogen; however, only 2 compared it to oral estrogen. <sup>(42,47,49)</sup> Nabhan showed that TD estrogen confers an advantage over oral estrogen for lumbar BMD at 12 months, while Torres-Santiago showed no difference between groups. These contradictory results are likely due to small and different patient populations: Nabhan evaluated prepubertal girls receiving induction, while Torres-Santiago evaluated postpubertal girls on maintenance doses of estrogen.

**Side effects:** There were no side effects reported in either group. This is likely due to the young age of the patients as well as the short duration of the studies. Larger and longer-term studies are needed to determine if the benefit of reduced DVTs shown in postmenopausal women taking TD vs. oral estrogen occurs in this population as well, particularly since TS patients are at higher risks of DVTs.

### **Critical Points of Evidence\***

#### **Evidence Supports**

- Utilize antimüllerian hormone (AMH) and inhibin B as early markers of ovarian failure. <sup>(1-10)</sup> – Weak recommendation, very low quality evidence
- Start estrogen close to the age of 12 years to maximize growth, as long as height prediction is adequate. <sup>(10-40)</sup> – Strong recommendation, low quality evidence
- Consider delaying puberty induction to the age of 14 years in patients with severe short stature. <sup>(10-40)</sup> – Weak recommendation, very low quality evidence
- Transdermal estrogen is preferred over oral estrogen for puberty induction. <sup>(41-50)</sup> – Weak recommendation, very low quality evidence

#### **Evidence Against**

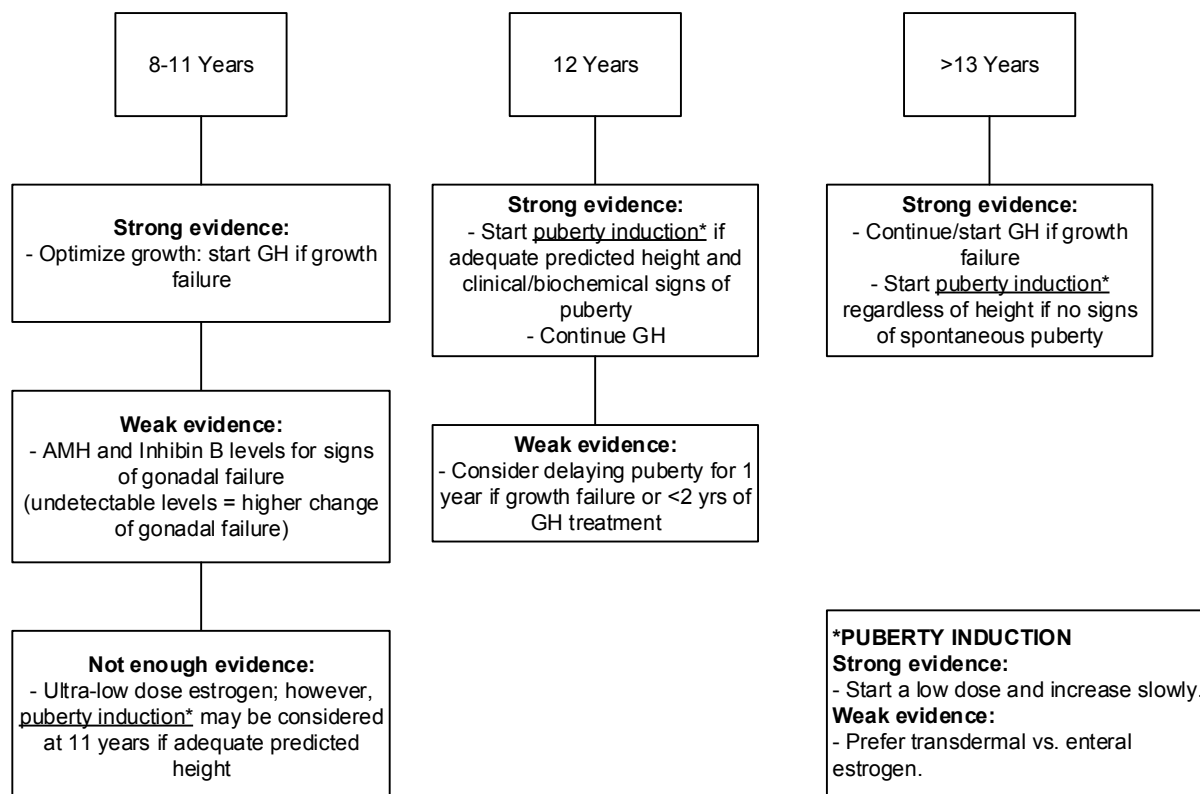
- Do not use FSH as an early marker of ovarian failure. <sup>(1-10)</sup> – Weak recommendation, very low quality evidence

\*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

### **Measures**

- Final height
- Age of thelarche
- Age of menarche
- Bone mineral density
- Uterine size, volume, and shape
- Side effects

## TCH Evidence-Based Outcomes Center Turner Syndrome



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### Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

### **EBP Course Participant and EBOC Support**

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### Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
  - PICO questions established
  - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
  - N/A
3. Literature Review of Relevant Evidence
  - Searched: PubMed, Cochrane
4. Critically Analyze the Evidence
  - 12 randomized controlled trials and 22 nonrandomized studies
5. Summarize the Evidence
  - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in a Puberty Induction in Girls with Turner Syndrome evidence-based review manual within EBOC.

### Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.

**"Evidence Supports"** provides evidence to support an intervention

**"Evidence Against"** provides evidence against an intervention.

**"Evidence Lacking/Inconclusive"** indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence*.

The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
<b>STRONG</b>	Desirable effects clearly outweigh undesirable effects or vice versa
<b>WEAK</b>	Desirable effects closely balanced with undesirable effects
Quality	Type of Evidence
<b>High</b>	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
<b>Moderate</b>	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
<b>Low</b>	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
<b>Very Low</b>	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

### Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the management of puberty induction in girls with Turner Syndrome. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

### Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

### Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient's family, to make the ultimate judgment regarding care.

### Version History

Date	Action	Comments
Jan 2016	Originally completed	