

**Feminization of Girls with
Turner Syndrome:
Much to be Considered**

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Conflict of Interest Disclosure

No conflict of interest to disclose

Objectives

Learner will be able to describe:

- General overview of TS
- Premature ovarian insufficiency(POI) in Turner syndrome (TS)
- Presentation of POI and diagnostic work up of POI
- Treatment options for POI
- Family resources related to feminization and ovarian insufficiency in TS

Background

- Turner syndrome (TS): genetic disorder in females resulting from complete or partial absence of the second X chromosome
- Random genetic occurrence
- Incidence: 1 in 2,500 live female births
- Approximately 50,000 women in US
- Clinical presentation can be quite variable
- 45 XO- classic karyotype
- Mosaic karyotype can present with more mild presentation but wide variation can be seen

(Bondy, 2001)

Meeting one child with TS is meeting JUST one child with TS



Presentation of TS by Age Group

Age group	Findings leading to diagnosis
Fetal	<ul style="list-style-type: none"> ▪ prenatal testing (cell free DNA and gender testing) ▪ ultrasound findings: cystic hygroma, nuchal folds, cardiac or renal anomalies
Newborn	<ul style="list-style-type: none"> ▪ cardiac or renal anomaly ▪ lymphedema ▪ phenotypic features
School age	<ul style="list-style-type: none"> ▪ growth failure ▪ short stature
Early adolescence and Late adolescence	<ul style="list-style-type: none"> ▪ short stature ▪ lack of pubertal onset ▪ pubertal arrest ▪ irregular menses ▪ primary or secondary amenorrhea

(Bondy, 2001)

Hallmark Features of TS

- **Short stature (98%):**
 - Slow rate of growth in toddlerhood, school age years and reduced pubertal growth spurt
 - Average final height 4'8"
- **Primary Ovarian Insufficiency (POI) (95 %):**
 - May present as:
 - Complete lack of spontaneous pubertal development
 - Spontaneous pubertal onset followed by arrested progression
 - Full pubertal development followed by amenorrhea (primary or secondary)
 - Fertility issues

(Bondy, 2001)

Other Features of TS

- **Cardiac anomalies:**
 - Bicuspid aortic valve
 - Coarctation of aorta
- **Renal anomalies:**
 - Duplex collecting system
 - Horseshoe shaped kidney
- **Ear & Hearing issues:**
 - Conductive or Sensorineural hearing loss
 - Otitis media
- **Autoimmune disease**
 - Thyroiditis
 - Celiac Disease
- **Facial anomalies:**
 - Micrognathia
 - Ptosis
 - High arched palate & crowding
 - Low set ears
 - Low hairline
- **Bone structure anomalies:**
 - Cubitus valgus
 - Short 4th metacarpals/tarsals
 - Scoliosis
- **Normal Intelligence**
- **Increased incidence of Learning Deficits:**
 - Visual spatial, processing speed, working memory
 - Difficulty with math
 - Social cognition deficits

(Bondy, 2001)

Presentation of POI in TS

- 30-40% of girls with TS will experience spontaneous onset of puberty
- Others may have no spontaneous onset
- Pubertal onset may progress but then subsequently arrest
- In patients with spontaneous pubertal onset, menarche may or may not occur spontaneously
- If menarche occurs spontaneously, it may continue for years or arrest (secondary amenorrhea)

Diagnostic Testing for POI

- Streak ovarian tissue results in primary ovarian insufficiency
- If no signs of breast development by age 12 years
 - assess gonadotropins (LH, FSH)
 - obtain bone age (as baseline)
- Arrested puberty (lack of progression in breast development, primary amenorrhea, secondary amenorrhea)
 - assess gonadotropins (LH, FSH)

Variables to Consider in Treating POI

Clinical implications:

- Final height outcome
- Impact on bone health
- Psychosocial implications of delayed pubertal onset

Treatment Implications:

- Formulation choice
- Dose at initiation of treatment
- Rate of dose progression

Historical Approach to Feminization

- Delay initiation of estrogen to achieve best final height
- Minimal focus on bone accrual and bone health
- Premarin (conjugated equine estrogen): commonly used estrogen preparation
- Provera (progesterone): commonly used as progesterone option
- Oral contraceptive pill (OCPs): hormone replacement option in older adolescents once fully feminized

Current Guidelines for Feminization: (Turner Syndrome Consensus Study Group)

- Start close to age 12 years if elevated gonadotropins and no signs of pubertal changes
- Start with low dose estrogen
- Progress dose slowly
- Goal: complete feminization over 2-3 years
- If bleeding occurs, add progesterone
- Monitor clinical signs of pubertal progression: progression of breast development, vaginal bleeding

Considerations Regarding Estrogen Replacement

- Psychosocial Implications
 - Puberty at age similar to peers
- Bone health and estrogen
 - Age of initiation
 - Dose escalation and formulation
- Various forms of estrogen formulations/delivery
 - More delivery options available
 - Pros and cons in terms of formulations

Considerations Regarding Estrogen Replacement

- 17 beta estradiol (E2) is preferred formulation
 - Most identical to natural estrogen
 - Plant derived
- Transdermal delivery
 - No stimulatory effect of liver proteins when given TD
 - Bypass the liver
 - Less impact on clotting
- OCPs may not provide adequate estrogen dose to meet the requirements of the female adolescent for bony accrual
 - Newer formulations of OCPs have less estrogen

Considerations Regarding Estrogen and Bone Health

- Estrogen is critical to optimize bone mineral accretion in adolescents with TS
- Low BMD and osteoporosis occurs earlier in women with TS
- Risk of fractures in TS women is 2-3 times higher than general population

Hormone Replacement Options

Estrogen Formulations

Formulation: active ingredient	Delivery	Effect	Dose increments	Brand names
17 Beta estradiol (E ₂) Natural estrogen	Oral TD	Identical to product of gonad Most physiologic Plant derived Can be measured commercially Less effect of liver proteins No stimulatory effect of liver proteins when given TD Transdermal: Costly 1991: first designed 1995: improved; better adhesive, able to cut, more steady delivery	Estrace tablets: 0.5, 1, 2 Menostar: 14 mcg patch Vivelle Dot: 25-37.5-50-75-100-200 mcg patch applied <u>twice</u> weekly Climara: 25-37.5-50-60-75-100 mcg patch applied weekly	Oral: Estrace Transdermal: Estraderm* VivelleDot Menostar Climara** * RESERVOIR: rate controlled - cannot be cut **MATRIX: Drug & polymer pad applied to skin - can be cut

Estrogen Formulations

Formulation: active ingredient	Delivery	Effect	Dose increments	Brand names
Estradiol Valerate (E ₂ V) Natural estrogen	Oral IM	In combined OCPs Plant derived: soy and yams Metabolized to 17 beta estradiol and valeric acid Absorbed more slowly & lasts longer	Oral: 0.5, 1, 1.5, 2 mg	Delestrogen

Estrogen Formulations

Formulation:	Delivery	Effect	Dose increments	Brand names
Ethinyl-Estradiol	Oral IM	in OCPs available 1954 Potent: 8-10 X estradiol Plant: soy & yams First pass GI 90% Absorbed upper GI Hepatic: liver proteins Long half-life extends hepatic effects	20, 30 or 50 mcg 20 and 30 mcg common amount in OCPs	Only available in combination with progesterone
Conjugated equine estrogen (CEE)	Oral IV cream	Pregnant mares Most non-physiologic Contains primarily estrone sulfate, equilenin sulfate, equilenin sul Contains 100 forms of estrogen compounds	0.3, 0.625, 0.9, 1.25 mg	Premarin, Cenestin, Enjuria

Progesterone

Formulation: active ingredient	Delivery	Effect	Dose increments	Brand names
Progesterone	oral	Micronized: increases bioavailability Plant source identical to progesterone produced by ovary metabolized by liver	100 mg 200 mg 300 mg Adult dose: 100- 200 mg/day X 10 days	Prometrium
Medroxyproge- sterone acetate	Oral Intramuscular (IM) subQ	Synthetic variant Metabolized by liver	Oral: 2.5 mg 5 mg 10 mg	Provera-oral Depot Provera- IM

Comparison: Oral versus Transdermal Estrogen

Oral	Transdermal
Plasma estrogen peaks & troughs • First pass through GI tract & liver (requires higher dose) • Increased hepatic enzymes, inflammatory markers • Increased triglycerides • Increased blood pressure • Reduced IGF-1 • Decreased LDL cholesterol and increased HDL	Serum Ez levels relatively constant • Does not pass through liver – lower doses required • No change in inflammatory markers • No change or decrease in triglycerides • Decrease in blood pressure • No effect on GH/IGF-1 • Decreases LDL but no change in HDL
<small>www.empr.com/clinical-charts/oral-and-transdermal-estrogen-dose-equivalents/article/266787/</small>	

Talking to Teens: Starting Estrogen

Golden Rules:

- Answer the question being asked
- Accurate and honest
- Concrete: what, when, where

Top 5 Commonly Asked Questions

- #1 When can I go buy a bra?
- #2 Where on my body will I put the patch?
- #3 Can I go in the swimming pool this summer??
- #4 Can I tell my friends I wear a patch?
- #5 When will my period start?

Nursing Implications: Patient/Family Education

- Expectations:
 - Breast development
 - Breast tenderness
 - Vaginal discharge and/or spotting
 - Moodiness
 - Pubertal progression
- Instruction on administration of estrogen & progesterone
- Set the ground work early-gradually over several visits

Nursing Implications: Patient/Family Education

- Long term implications of estrogen:
- Bone health
 - Maintenance of secondary sexual characteristics
 - Importance of regular periods
 - Reproductive health
 - Fertility preservation options (if applicable)

Anticipatory Guidance for Parents



Diverting, dodging, sending them elsewhere



Assuming we know what they need

Supporting the Parent: Um...what if !?!

- Accept that there is no one perfect way or one perfect answer
- Encourage meeting with counselor/LCSW early on
- Role play: talk ahead of time about how and what to say
- Be prepared but realize it may not go as planned
- Tailor it: parents know their child best
- Provide support and resources

Resources and Support

- Therapist trained to deal with:
 - Adolescent related issues
 - Coping mechanisms
 - Chronic illness and teens
 - Disclosure of diagnosis: parent and child
 - Acceptance
 - Parenting skills
- Educational resources
 - Turner Syndrome Society
 - Turner Syndrome Foundation
 - Lay resources that provide overview on puberty
 - Care and Keeping of Me and others books in the series (American Girl series)
 - What's Happening to Me

Summary

- Estrogen is standard treatment of POI in TS
- Estrogen is essential for pubertal process, bone health and psychosocial well being
- Bone health is a critical variable to be considered in estrogen treatment decisions
- Patients and family require guidance, education and support

Thank you

References available upon request
