Estrogen Replacement in Turner Syndrome: Literature Review and Practical Considerations

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Context: Most girls with Turner syndrome (TS) have hypergonadotropic hypogonadism and need hormonal replacement for induction of puberty and then for maintaining secondary sex characteristics, attaining peak bone mass, and uterine growth. The optimal estrogen replacement regimen is still being studied.

Evidence Acquisition: We conducted a systematic search of PubMed for studies related to TS and puberty.

Evidence Synthesis: The goals of replacement are to mimic normal timing and progression of physical and social development while minimizing risks. Treatment should begin at age 11 to 12 years, with dose increases over 2 to 3 years. Initiation with low-dose estradiol (E_2) is crucial to preserve growth potential. Delaying estrogen replacement may be deleterious to bone and uterine health. For adults who have undergone pubertal development, we suggest transdermal estrogen and oral progestin and discuss other approaches. We discuss linear growth, lipids, liver function, blood pressure, neurocognition, socialization, and bone and uterine health as related to hormonal replacement.

Conclusion: Evidence supports the effectiveness of starting pubertal estrogen replacement with low-dose transdermal E_2. When transdermal E_2 is unavailable or the patient prefers, evidence supports use of oral micronized E_2 or an intramuscular preparation. Only when these are unavailable should ethinyl E_2 be prescribed. We recommend against the use of conjugated estrogens. Once progestin is added, many women prefer the ease of use of a pill containing both an estrogen and a progestin. The risks and benefits of different types of preparations, with examples, are discussed. (***J Clin Endocrinol Metab*** **103: 1790–1803, 2018)**

The 2017 updated guidelines from the International Turner Syndrome Consensus Group have been published in the European Journal of Endocrinology (1) and endorsed by the European Society of Endocrinology, the Endocrine Society, the Pediatric Endocrine Society, the European Society for Pediatric Endocrinology, the European Society of Human Reproduction and Embryology, the American Academy of Pediatrics, and the Society for Endocrinology (United Kingdom). The American Heart Association and European Society of

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Abbreviations: AMH, anti-Müllerian hormone; BMD, bone mineral density; CEE, conjugated equine estrogen; E_2, estradiol; EE, ethinyl estradiol; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; OC, oral contraceptive; TD, transdermal; TS, Turner syndrome; VTE, venothrombotic episode.

Cardiology also had official delegates at the meeting. The present paper expands on those guidelines specifically relating to puberty and estrogen replacement.

Turner syndrome (TS) defines phenotypic females who have one X chromosome and complete or partial absence of the second X chromosome. TS is characterized by physical features, including a classic facial appearance, neck webbing, short stature, and lymphedema, as well as ovarian insufficiency, sensorineural hearing loss, congenital cardiovascular disease, renal anomalies, some neurodevelopmental disorders, and increased risk of thyroid and celiac diseases. TS affects 25 to 50 girls per 100,000, and there is a very broad clinical spectrum of presentation. Some individuals have all the aforementioned features and others have minimal features, with or without short stature and ovarian insufficiency. The karyotype in TS ranges from complete 45,X to forms of mosaicism in which there is a normal (*i.e.*, 46,XX or 46,XY) cell line, and an abnormal second (or third) cell line (2).

TS is usually accompanied by hypergonadotropic hypogonadism due to gonadal dysgenesis and ensuing primary or secondary amenorrhea. Therefore, most patients with TS will need hormonal replacement therapy, first for induction of puberty and then for maintaining secondary sex characteristics, attaining peak bone mass, and normalizing uterine growth for possible pregnancy later. This review focuses primarily on estrogen hormone replacement in the care of girls with TS.

The optimal estrogen replacement therapy regimen to induce pubertal development and maintain beneficial effects in adults is still being studied. A substantial body of literature to date supports the effectiveness and theoretical benefits of starting pubertal estrogen replacement with low-dose transdermal (TD) estrogen, although, to our knowledge, there is no study to date of TD use from initiation of puberty until adulthood. Theoretical benefits of TD use include the more physiologic route of delivery, avoiding first-pass effects in the liver that include the accumulation of unphysiologic estrogens observed after the oral route (3), and avoiding effects associated with a procoagulation state (4) and increased risk of stroke (5).

We review estrogen forms, timing of replacement, dosing, route of administration, duration of treatment, and monitoring of treatment. We also review evidence relevant to optimizing the outcome and minimizing the risk of estrogen replacement in puberty as regards growth, lipids, liver health, bone health, uterine health, and thrombosis risk, as well as socialization and neurocognitive benefits.

Spontaneous Puberty in Girls With TS

Approximately one-third of girls with TS have spontaneous breast development that may progress to menarche, occurring most often in girls with mosaicism (6, 7). Regular menstrual cycles occur in ~6% (8) of these young women.

Laboratory Markers of Ovarian Function

Elevated concentrations of gonadotropins, luteinizing hormone (LH), and, particularly, follicle-stimulating hormone (FSH) indicate ovarian failure (9, 10). FSH concentrations are higher in girls with 45,X karyotype compared with those with mosaic karyotype. LH and FSH levels in girls with TS are elevated after birth, then decline to levels similar to girls with normal ovarian function during mid childhood, and rise again in the peripubertal years (9, 11) or at the time of loss of previous ovarian function. Low anti-Müllerian hormone (AMH) levels and undetectable inhibin B levels have been reported to predict ovarian failure in TS (9, 12). In one study, 70 girls with TS and 2406 girls without TS had LH, FSH, and inhibin B concentrations measured before estrogen treatment (9). Ovarian function was related to whether girls had 45,X or a mosaic karyotype. According to the study data, undetectable inhibin B may predict the absence of spontaneous puberty, but the specificity was low. AMH in 120 girls with TS predicted no ovarian function when levels were <4 pmol/L (0.56 ng/mL) and predicted ovarian function when levels were >19 pmol/L (2.66 ng/mL) (12).

Treatment Options for Induction of Puberty and Maintenance of Feminization

Estrogen forms available for replacement

Estradiol (E_2) is the natural form of estrogen that is secreted and binds to the estrogen receptor in humans (13). Ethinyl estradiol (EE) is a very potent synthetic E_2 analog that is not metabolized to E_2. It binds to estrogen receptors α and β. EE has an ethinyl group covalently attached at the 17α-position. EE is taken up in unmodified form and retained by estrogen target tissues for a longer time than is E_2. The E_2 precursor estrone acts after being metabolized to E_2. Equine estrogens, the major components of the widely used conjugated equine estrogens (CEEs), consist of >100 forms of estrogens of different receptor affinity and potency. Estrogens are metabolized in the liver by microsomal cytochrome P-450 with aromatic hydroxylation at either the C2 or C4 position as the major route. Other pathways include formation of glucuronide conjugates and sulfation (14–16).

Table 1 lists commonly available, lower-dose estrogen treatments for pubertal induction and considerations for their use. Table 2 lists some common progestin and estrogen/progestin combination replacement options after pubertal

Table 1. Some Common Low-Dose Estrogen Treatment Options for Pubertal Induction in TS and Considerations for Use

Preparation[a]	Doses Available, Frequency, Route	Starting Dose at Puberty	Dose Increase Approximately Every 6 Mo to Adult Dosing	Considerations for Use
Transdermal options (some brands)		3–7 μg/d	25–100 μg/d	See text on applying patches
Menostar (Bayer) (matrix)	14 μg weekly TD	One-half patch weekly	Only used for low dosing, not full replacement	Easiest way to give low dose; once a week dosing
Vivelle Dot (Novartis) (matrix)	25, 37.5, 50, 75, 100 μg twice weekly	One-quarter patch weekly, or one patch per month (no patch other 3 weeks)	25–100 μg twice weekly	Designed for twice-weekly dosing, but can give once per week to increase dose more slowly
Vivelle Mini (matrix)	25, 37.5, 50, 75, 100 μg twice weekly	Too small to cut consistently	25–100 μg twice weekly	Smaller size patch, but not smaller dosing
Generic (different brands in different countries)	25, 37.5, 50, 75, 100 μg twice weekly	One-quarter patch weekly, or one patch per month (no patch other 3 wk)	25–100 μg twice weekly	Once-weekly dosing can be used.
Estraderm (matrix)	50, 100 μg twice weekly	Not small enough to initiate puberty	50–100 μg twice weekly	Cannot use to initiate puberty
E_2 gel		0.25 mg per pump	One pump daily	Only available in some countries at the low dose
Estragel (Ascend), 0.06%	0.75 mg E_2 per pump			
Divigel (Vertical), 0.1%	0.25, 0.5, 0.1 mg E_2 per pump			
Oral options				
17β-E_2 [*e.g.*, Estrace (Allergen), Cetura (ACE)]	0.5, 1, 2, 4 mg/d	One-half pill daily	1–4 mg/d	Cheapest option, brands vary by country
EE		2 μg/d	10–20 μg/d	Not available in many countries
Premarin (Pfizer) (a CEE)	0.3, 0.625, 0.9, 1.25 mg/d	One-half pill daily	0.625–1.25 mg/d	Not available in many countries, not recommended based on safety
Depot options				
Depot E_2 (E_2 cypionate)	5 mg/mL	0.2 mg/mo	2 mg/mo	Not available in Europe

[a]The reader should be aware that availability and trade names differ among countries. The list is not all inclusive.

induction is complete. The reader should be aware that availability and trade names differ among countries. The list is not all inclusive. We present data from various routes and preparations but list other preparations for reference, with the caution that studies have not been done in TS with each preparation listed. Table 3 summarizes published low-dose estrogen treatments for puberty induction in TS.

Timing and dose

The goals of replacement are to mimic the normal progression of puberty in girls while maximizing growth potential and minimizing risks. Delaying estrogen replacement may be deleterious to bone, uterine, and psychosocial health parameters (28). To mimic normal physical and social development, initiation of treatment should begin at 11 to 12 years of age if levels of gonadotropins are elevated or AMH concentration is low. LH and FSH levels may be measured yearly starting at age 11, based on average age of pubertal onset. If gonadotropin concentrations are normal for age, observation for spontaneous puberty is appropriate, with future replacement therapy if gonadal failure occurs.

Incremental dose increases at ~6-month intervals can mimic the normal pubertal tempo until adult dosing is reached over 2 to 3 years. This theoretically translates into a 25% to 100% increase in dose every 6 months for four to six dose changes between the initiation and adult doses portrayed in the Table 1. However, no studies to date have rigorously studied outcomes in relation to the rate of dose increase for the different preparations.

In general, the studies summarized in Table 3 report onset of breast buds within 6 months in most girls (17, 18, 22, 23, 27). Each of these regimens results in pubertal stage 4 breasts in an average of 2.25 years, which is

Table 2. Some Common Progestin and Estrogen/Progestin Combination Replacement Options After Pubertal Induction Is Complete

Adding Progestin Options	Doses Available, Frequency and Route	Not Needed to Initiate Puberty	Add Once Bleeding Occurs or After 2 Years	Notes
Medroxyprogesterone acetate	10 mg/d for 10 d		Give with TD E_2 or alone for 10 d	
Micronized progesterone (Prometrium; AbbVie)	100 mg/d		Give continuously with TD E_2	Less breast cancer risk long term
Combined E_2/progestin sequential patch (some brand options)		Do not use to initiate puberty		
Climara Pro (Bayer)	E_2 0.045 mg and levonorgestrel 0.015 mg/24 h		One patch weekly	
Combipatch (Noven)	E_2 0.045 mg and norethidrone 0.14 or 0.25 mg/24 h		One patch weekly	
Evo-Sequi (Janssen)	E_2 50 μg and norethisterone acetate 170 μg/24 h		Two patches weekly	
Combined E_2/progestin sequential pills		Do not use to initiate puberty		
Trisequens (Novo Nordisk)	E_2 2 mg and norethisterone acetate 1 mg		1 pill/d	
Divina plus	Estradiolvalerate 2 mg and medroxyprogesterone acetate 10 mg		1 pill/d	
Femoston (Mylan)	E_2 and dydrogesterone 1/10 or 2/10 mg		1 pill/d	
Oral contraceptive pills[a]		Do not use to initiate puberty		

[a] There are multiple types of oral contraceptive pills, which differ in estrogen dose, sequential vs continuous, and type and dose of progestin. The reader is referred to the text to outline general principles.

similar to that in girls with TS who have spontaneous puberty (1.9 years), as well as in the general population (23).

Girls with TS are very short and have a very short adult-height potential, typically 20 cm less than the average female population in all countries studied. Growth hormone (GH) treatment is US Food and Drug Administration–approved therapy to promote growth in these girls, and the earlier it is started, the better the growth promotion. However, the expectations of intervention are modest. In general, GH therapy results in a net gain of 1 cm/y of treatment (20, 29). In girls in whom GH treatment has been delayed, consideration of initiation of GH prior to low-dose estrogen is particularly important to optimize growth. There are no data to support the specifics of timing in such cases; rather it is a matter of individualized judgment, balancing the desire for taller height vs the desire for more rapid feminization. When height is a greater concern, often GH treatment can be initiated before low-dose E_2; however, we recommend that E_2 not be delayed past 14 years of age. When feminization is a greater concern, GH and E_2 can be started simultaneously.

Initiation with low doses of E_2 is crucial to preserve growth potential even if GH treatment has already been initiated. Very low doses of EE and E_2 do not interfere with growth response to GH therapy when started at ≤12 years of age (21, 24).

Progestins

Patients with TS have a normal uterus anatomy, so progestin must be added once breakthrough bleeding occurs, or after 2 years of E_2 treatment, to minimize the risks of endometrial hyperplasia, namely, irregular bleeding and endometrial cancer associated with prolonged unopposed estrogen (30, 31).

Progestins are divided into several classes (Table 4) and individual agents can bind to the progesterone receptor as well as the androgen, glucocorticoid, and mineralocorticoid receptors (32). Each progestin exerts differential effects on these various receptors and, accordingly, unique, nonclass action effects. In addition to the progestational effects, the 19-nor-progesterone derivatives are associated with androgenic action, medroxyprogesterone acetate with glucocorticoid-agonistic action, and drospirenone with antiandrogenic and anti-mineralocorticoid actions, whereas progesterone is more specific to progestational effects. The combined oral contraceptives (OCs) containing progestins are divided into first-, second-, third-, and fourth-generation OCs. First-generation OCs contain 50 μg of the estrogen mestranol and the progestogen norethynodrel (*e.g.*, Enovid; Searle). Most later-generation pills use 20 to 35 μg of EE as the estrogen. Second-generation progestogens include norethindrone; its acetate, ethynodiol diacetate; and levonorgestrel.

Table 3. Summary of Published Studies of Low-Dose Estrogen Treatment of Puberty Induction in TS

Reference, Year	Subjects	Estrogen Treatment, Route and Dose	Outcomes	Height
Ankarberg-Lindgren *et al.* (17), 2001	n = 8 girls with TS (age 12–16 y) and n = 7 with other hypogonadism	TD E_2 6–18 μg given just 12 h overnight	B2 in 3–6 mo in 75% of girls on low-dose, and B3 in 2 y on higher dose; TD dose correlated with serum E_2 ($P < 0.001$)	No height data
Van Pareren *et al.* (18), 2003	n = 60 girls with TS with or without spontaneous puberty	Oral E_2 5 μg/kg × 2 y → 7.5 μg/kg × 1 y → 10 μg/kg after 4 y GH	B2 onset in 0.2 y on average	No negative effect on height or growth velocity vs spontaneous puberty
Piippo *et al.* (19), 2004	n = 23 girls with TS	E_2 gel 0.1 mg × 1 y → 0.2 mg × 1 y → 0.5 mg × 1 y → 1 mg × 1 y → 1.5 mg × 1 y	Pubertal advance about one stage per year treatment with 50% B2 at 6 mo	Adult height 153.1 ± 4.8 cm (mean ± standard deviation)
Soriano-Guillen *et al.* (20), 2005	n = 704 girls with TS with or without spontaneous puberty	Oral EE 1–5 μg/d; oral E_2 0.5 mg/d; TD one-quarter of a 25-μg/d patch	No data on rate of pubertal progression	Patients receiving TD E_2 were taller than those receiving oral formulation by an average 2.1 cm, but shorter than spontaneous
Rosenfield *et al.* (21), 2005	n = 14 girls with TS, compared with NCGS registry, age 12–15 y	Depot E_2 0.2 mg/mo with increase of 0.2 mg every 0.5 y; GH also given 0.05 mg/kg/d	Half of girls B1 → B2 in 0.5 y, and increased one stage per 0.5 y with each 0.2-mg increase in dose. with 1 mg dose: 100% B3–B5 by 2 y and menarche in 62.5% by 2.5 y	Lowest dose had greatest GV; FH > PAH at start of treatment; FH > GH alone, growth not as good as in TS with spontaneous puberty
Nabhan *et al.* (22), 2009	n = 12 girls with TS, age 11.3–17 y	Oral CEE (0.3–0.45 mg/d) vs TD (25 μg/d for 6 mo → 37.5 μg/d for 6 mo)	B3–4 by 1 y in 83%; no change in 17%; TD group had greatest increase in spine density, BMD, uterine length and volume	No height data
Bannink *et al.* (23), 2009	n = 56 girls with TS, age 11–18 y	Oral E_2 (5 μg/kg/d) × 2 y, with progression to 7.5 and 10 μg/kg/d	Breast stage progressed in same timing as average Dutch population: B1 → B2 in 0.2 y; B1 → B4 in 2.1 y	No height data
Torres-Santiago *et al.* (3), 2013	n = 40 girls with TS, age 13–20 y	Oral E_2 (average, 2 mg) vs TD E_2 (average, 0.1 mg), dose titrated to plasma E_2	No difference in body composition, BMD, or lipids between groups	No height data
Ross *et al.* (24), 2011; Quigley *et al.* (25), 2014	n = 144 girls with TS analyzed for growth; n = 123 girls with TS analyzed for puberty, age 5–12.5 y	Oral EE: 25 ng/kg/d, 5–8 y; 50 ng/kg/d, >8–12 y; >12 y, escalating from 100 ng/kg/d; with or without GH	EE dose decreased for breast development before age 12 y or vaginal bleeding before age 14 y; age of menarche similar to general population; earlier breast development for girls who received the early low dose	GH plus EE group height SDS increase of 0.58 compared with increase of 0.26 in GH alone
Perry *et al.* (26), 2014	n = 92 girls with TS, age 7–13 y	Oral EE: 2 μg/d year 1; 4 μg/d year 2; 6/8/10 μg/d increases every 4 mo in year 3	B1 → B2 in 0.65 y and to B4 in 2.25 y	Growth reported to be not as good as with depot E_2
Çakir *et al.* (27), 2015	n = 13 girls with TS, age 11–17 y	Oral E_2 0.5 mg/d vs TD 4.5 μg/d	B1 → B3–4 in 1 y	BA advanced less with TD (ΔCA/ΔBA 2.2 vs 0.58; $P = 0.005$); GV greater on TD at 1 y (4.35 vs 3.8; $P = 0.022$)

Abbreviations: B2, breast stage 2; B3, breast stage 3; B4, breast stage 4; BA, bone age; CA, chronologic age; FH, final height; GH, growth hormone; GV, growth velocity; PAH, predicted adult height; Δ, change in; SDS, standard deviation score.

Third-generation progestogens include desogestrel, norgestimate, and gestodene. Fourth-generation pills include drospirenone. All OCs increase the risk of venothrombotic episodes (VTEs). A recent guideline (33) concluded that combinations of EE with the third- or fourth-generation progestogens have a slightly higher risk of VTE than those containing first- and second-generation components. Micronized progesterone is associated with a lesser risk (34).

Regimens of estrogen plus a progestin are either combined sequentially with an estrogen for 21 to 25 days and the progestin for only 10 to 14 days, or combined with both sex steroids continuously. The estrogen is given for up to 21 to 25 days to cause the endometrium to

Table 4. Classification of Progestins

Classification	Progestin
Natural	Progesterone
Synthetic	
Pregnane derivatives	
Acetylated	Medroxyprogesterone acetate
	Megestrol acetate
	Cyproterone acetate
Nonacetylated	Chlormadinone acetate
	Dydrogesterone
	Medrogestone
19-Norpregnane derivatives	
Acetylated	Nomegestrol acetate
	Nesterone
Nonacetylated	Demegestone
	Promegestone
	Trimegestone
Nor-testosterone	
Ethinylated estranes	Norethindrone (norethisterone)
	Norethindrone acetate
	Ethynodiol diacetate
	Norethynodrel
	Lynestrenol
	Tibolone
13-Ethylgonanes	Levonorgestrel
	Desogestrel
	Norgestimate
	Gestodene
Nonethinylated	Dienogest
	Drospirenone

become proliferative; the progestin in combination with the estrogen induces the luteal phase of the endometrium. Ten days of a progestin each month protects against estrogen-induced endometrial hyperplasia, and 3 months of combined continuous estrogen plus a progestin is also protective (35). The combined sequential regimens are associated with menstruation and are preferred in younger women, whereas the combined continuous regimens prevent uterine bleeding, an attractive factor for older women. Intrauterine devices containing a progestin block endometrial hyperplasia and unwanted bleeding, can be used along with an estrogen, and can be especially attractive for women with bleeding problems who are taking either TD or oral combined formulations. Availability of products varies by country (Table 2).

Route: Oral vs TD Comparisons

E_2 is normally secreted into the systemic circulation, the liver receives the same dose as other somatic tissues, and a systemic route of estrogen delivery is physiologic (13). In contrast, estrogen given orally reaches the systemic circulation only after absorption into the portal venous system and metabolism by the liver, thus exposing the liver to a greater dose of estrogen than the rest of the body.

TD E_2 is the most widely used of the physiologic E_2 options, but the commercially available forms (patches and gels) are designed for the adult female market and, thus, the lowest-dose forms are four- to 10-fold greater than are appropriate to deliver early pubertal E_2 blood levels. The main strategies that have been advocated to fractionate TD E_2 in a manner appropriate for early puberty are based on different perspectives on normal pubertal E_2 physiology.

Currently, the lowest-dose patch commercially available delivers 14 μg/d E_2, and the most widely used low-dose patches deliver 25 μg/d. One method to deliver lower doses is to cut the patch in smaller pieces. Patches with a matrix design can be easily cut, whereas patches with a reservoir technology should not be cut. The disadvantages of cutting patches are that handling the smaller pieces may be difficult and cutting the patches is not recommended by the products' labels. However, there is clinical experience with this, especially in Scandinavia. There, a group showed that a fractionated patch dose (one-quarter patch of a 25-μg dose approximately equals 6.2 μg or even less) applied overnight mimicked the normal, early-morning serum E_2 peak and fell back to baseline within a few hours of patch removal (17). If one does not want to cut the patches, it has also been proposed that cyclic administration of patches, commencing with the application of a 14- to 25-μg patch for 1 week monthly may achieve similar results, although we have no data at this time with this method (21, 36). This proposal comes from an expert committee of the Pediatric Endocrine Society, which recommended initiating cyclic therapy with 25 μg/d TD E_2 for 1 week and then gradually increasing the duration of patch application to 3 weeks per month before increasing the patch size. Support for this recommendation includes not only considerations of convenience and manufacturer recommendations against patch fractionation but evidence of efficacy of cyclic administration of depot systemically delivered E_2 (21). Evidence also exists that estrogenization of the vaginal mucosa lags behind changes in serum E_2 by about 1 week (3, 37), suggesting that the pituitary-ovarian axis activity normally commences with attenuated cyclicity (38). Expert discussion of this method, however, suggests that 1 week with and 3 weeks without E_2 would cause such variable changes in plasma E_2 concentrations during these 4 weeks that may not mimic physiology. Additional data are needed before conclusions can be made regarding the optimum mode of patch-application recommendation.

Two studies by Torres-Santiago *et al.* and Taboada *et al.* have directly compared the TD and oral routes of E_2 administration in teenagers (3, 39). The pharmacokinetics and pharmacodynamics of different doses of E_2 given orally vs transdermally were examined in a group of girls with TS. TD E_2 results in E_2, E_1, and bioestrogen

concentrations that are closer to normal and achieve greater suppression of LH and FSH in lower doses compared with normally menstruating girls without TS (40). The metabolic effects of oral vs TD E_2 were additionally compared in 40 late-teen girls with TS followed for 1 year (3). The researchers found no differences in body composition, bone mineralization, or plasma lipids when the plasma E_2 levels were titrated to those of normally menstruating adolescents. Although no metabolic differences were observed, oral estrogen was associated with a marked increase in conjugated estrogen precursors such as estrone sulfate and increased serum estrogenic bioactivity. This is concerning in the context of the increased thromboembolic risk observed with oral estrogen in epidemiological studies, although there are no data to suggest that such problems are present in TS (discussed later in this article). Some European countries have approved an E_2 gel (Table 1), but it is very difficult to give a small enough dose for pubertal induction, and there is only one study with data from girls with TS (19).

Depot route

Results of a randomized controlled trial showed that early, depot E_2 monthly injections at very low doses stimulated normal pubertal growth and development in conjunction with GH treatment (21). This remains a viable alternative in the United States, although it is less attractive because of the pain of injection.

Practical Considerations

Estrogen treatment is crucial for girls with TS, first to induce puberty and then to maintain healthy levels for all the reasons described here. Individualizing treatment to optimize compliance is important, and helping girls understand how easy it is to help them have breast development consistent with their peers should be encouraged. Based on literature and theoretical principles presented here, we suggest the following practical approach to feminize girls with TS: initiate puberty with low-dose TD E_2, when available, starting with half of a 14-μg patch applied weekly, or a whole 14- or 25-μg patch for 1 week per month at age 11 to 12 years (Table 1), and increase every 6 to 12 months based on response and growth potential. When not available, or for physician or patient alternative preference, consider approaches discussed earlier in this article and listed in Tables 1 and 2.

For the adult patient with TS, no long-term studies have assessed the optimal dose, route, or duration of E_2 treatment, to our knowledge. Our recommendations are based on available data from women with TS and from other hypogonadal patients. The effects of hormone treatment in TS may be different from what is observed in other patient populations, and caution is needed when extrapolating data from postmenopausal studies (40). With those cautions, the type and route must be negotiated, taking into account the preference of the patient, the size of the uterus (for possible oocyte donation), bone and body composition assessed by dual-energy X-ray absorptiometry, blood pressure, and quality of life, as well as other considerations (discussed later in this article). Adult TD replacement doses of 50 to 150 μg/d or oral replacement doses of 2 to 4 mg of E_2 will often be sufficient. Oral progestin for 10 days per month (combined sequential approach) or continuous progestin regimens are suggested [analogous to the combined/continuous methodology commonly used for menopausal hormone therapy (41)]. If bleeding irregularities occur or if the patient prefers, an intrauterine progestin-coated device can be used together with either continuous oral or TD E_2. This will reduce bleeding irregularities and often abolish bleeding and the need for systemic progestin use. Close collaboration with a gynecologist with knowledge of TS is very useful.

Duration

Once adult replacement doses are reached, treatment should continue until the time of usual menopause, around age 51 to 53 years, when the risks vs benefits of continuing should be assessed, individualized, and reassessed annually (35, 41). Combined estrogen and progestin treatment duration is limited by increased risk of breast cancer (42); however, there are no clinical or epidemiological data relative to TS to suggest that breast cancer is a problem. Actually, breast cancer seems to occur less frequently among women with TS (1), although diminished overall estrogen exposure may be a factor. Estrogen therapy alone after menopausal age has a more favorable risk–benefit ratio, allowing more flexibility in duration, but is only indicated in women who have undergone hysterectomy (43). There often will be a continued need for education of the patient with TS to explain the beneficial effects of hormonal replacement therapy on multiple organ systems to maintain adherence to therapy.

Monitoring Treatment

Routine monitoring of serum LH or FSH levels is not recommended during estrogen treatment, because levels remain elevated in agonadal women until higher levels of estrogen are given (44). The suppression of gonadotropins was comparable after oral and TD E_2 use when doses were titrated to similar serum E_2 levels (3). E_2 measurement using a sensitive assay (*e.g.*, liquid or gas

chromatography with tandem mass spectrometry) allows dose titration if desired, though E_2 levels for optimal linear growth remain to be determined. Clinical assessment, patient satisfaction, patient age, and, often, residual growth potential are the primary determinants for dose increase. If potential for taller stature is still possible, girls may take lower estrogen doses for a longer time. If girls are already older at initiation, the duration until adult dosing may be shortened.

In adults, replacement TD doses of 50 to 200 μg/d typically allow women to reach normal adult plasma E_2 concentrations. The normal range of E_2 in cycling women is very wide, with early follicular phase levels as low as 20 to 40 pg/mL (~75 to ~150 pmol/L) and midcycle peak of 200 to 600 pg/mL (~730 to ~2200 pmol/L), and some experts replace to these levels (3). When oral estrogen is used, adult replacement doses of 2 to 4 mg of E_2 will result in normal circulating E_2 levels [*i.e.*, ~100 to ~155 pg/mL (~367 to ~568 pmol/L)] (44) and may lead to normal levels of FSH and LH in some women (44, 45). However, women with TS lack inhibin (46), so normalizing LH and FSH levels is not the goal *per se* (47, 48). Optimizing all the health benefits and minimizing the risks is the goal, and it is important to remember that this must be individualized.

Optimize Outcomes, Minimize Risks: Growth, Lipids, Liver, Bone Health, Uterine Health, and Thrombosis Risk

Estrogens and linear growth

Low-dose estrogen regimens do not appear to interfere with growth response to GH therapy when begun at 11 to 12 years of age at low doses (21, 24, 26, 49). Ultra-low dose oral EE (starting at 25 ng/kg/d at ages 5 to 12 years) in childhood TS has been reported but is not currently recommended, based on an increased risk of earlier thelarche and no proven benefit to growth or pubertal outcome (25).

A consistent effect of physiologic E_2 replacement on IGF-1 concentration has not been established (3). IGF-1 concentrations tended to be lower on oral than TD E_2 [-16 ± 12 vs 28 ± 12 ng/mL (mean ± standard error) at 12 months; $P = 0.059$] (3), whereas an earlier study from the same group showed no change in IGF-1 concentration after oral or TD therapy (50). TD application caused a decrease in IGF binding protein-3 and GH binding protein compared with an increase in the former and unchanged level of the latter after oral administration (51). In contrast, contraceptive doses of oral EE are known to suppress IGF-1 (52, 53). In a small study (n = 13 girls), bone age advanced less when using TD E_2 than oral E_2 (change in chronological age divided by change in bone age, 2.2 vs 0.58, respectively; $P = 0.005$). At the same time, growth velocity was greater when using TD E_2 than oral E_2 at 1 year (4.35 vs 3.8 cm/y, respectively; $P = 0.022$), suggesting overall better growth (17).

Estrogens and Metabolism

Lipids

Although there are theoretical reasons to be concerned about the relative systemic and hepatic hyperestrogenism of low-dose oral estrogens vs low-dose TD E_2, evidence thus far does not indicate that the hepatic effects on lipids or binding proteins cause an appreciable clinical difference between the two forms of treatment (Table 5) (3, 39, 54). With the exception of one study reporting significantly elevated high-density lipoprotein cholesterol after oral E_2 (54), there were no significant differences in lipids between groups with different routes of estrogen administration (3, 39).

Estrogen deficiency in TS is associated with elevated levels of intrahepatocellular lipids (62). Notably, whereas liver enzymes are elevated in untreated TS (45, 51, 63, 64), exogenous estrogen-progestin administered orally or transdermally reduces these levels (45, 52, 65). However, withdrawal of estrogen substitution did not influence liver enzyme levels (66, 67). There was no evidence of liver toxicity from estrogen replacement therapy (61).

Glucose and insulin

The risk of type 1 and type 2 diabetes mellitus is increased in patients with TS across all ages (68). However, there were no significant differences in glucose (3), insulin tolerance (57, 59), fasting insulin concentration, protein turnover and lipolysis (50), osteocalcin or highly sensitive C-reactive protein (3), body mass index, or waist-to-hip ratio (59, 60) between groups receiving TD vs oral estrogen treatment (Table 5). Glucagon and insulin levels (during oral glucose tolerance testing), as well as insulin resistance, tended to be lower after evening oral E_2 administration (0.3 to 0.5 mg/d) (58). Hyperinsulinemia was suppressed to normal by both EE and CEE. A recent study in 104 girls with TS who were followed up to 7 years after GH therapy showed no negative influence of GH treatment on β-cell function, which is also reassuring, because most of these girls continued on estrogen therapy (69).

Estrogens and bone density

Maintenance of bone health is crucial for women with TS. Delaying estrogen replacement is deleterious to bone health. Initiating and maintaining estrogen therapy during puberty and adulthood as outlined in this article is important for bone density accrual and prevention of

Table 5. Estrogen Treatment and Metabolic Outcome Data

Reference, Year	No. of Subjects	Treatment	Main Metabolic Measure Outcome
Jospe *et al.* (54), 1995	8	Oral E_2 100 ng/kg/d vs TD E_2 0.0125 mg/kg/d	Oral, but not TD, increased serum HDL
Gravholt *et al.* (55), 1998; Gravholt *et al.* (51), 1997	15 (oral) 8 (TD)	Oral: 2 mg/d E_2 days 1–22, plus 1 mg/d norethisterone acetate days 13–22, and 1 mg/d E_2 days 23–28 vs TD E_2 50 mg/d for 28 days plus oral 1 mg norethisterone days 13–22	No difference between oral and TD in insulin sensitivity, body composition changes, 24-h ambulatory blood pressure, IGF-1, liver function test results, and lipid levels
Gussinyé *et al.* (56), 2000	12	TD E_2 100 μg/d	BMD and BMD z-score values significantly increased; no significant differences in BMI, calcium intake, and physical activity habits
Guttmann *et al.* (57), 2001	17	CEE 0.625 mg/d vs EE 30 μg/d	Hyperinsulinemia was suppressed to normal by both EE and CEE Lipid profiles were normal on both regimens. PTH and 1,25-dihydroxyvitamin D levels increased while receiving HRT (EE > CEE), and phosphorus decreased Alkaline phosphatase, osteocalcin, and urinary deoxypyridinoline cross-links were high while off therapy; the former two suppressed to high-normal levels on the EE regimen, but not on CEE
Naeraa *et al.* (58), 2001	9	Morning oral E_2 6–11 μg/kg/d vs evening oral E_2 6–11 μg/kg/d	During OGTT in the morning, glucagon and insulin levels were lower after evening E_2 administration, and insulin resistance tended to be lower
Alves *et al.* (59), 2006	9	CEE 0.625 mg/d vs TD E_2 (gel) 1.5 mg/d	No difference in BMI, WHR, or insulin tolerance between CEE and TD E_2 During TD, tendency toward increased total lean mass
Mauras *et al.* (50), 2007	11	Low-dose oral E_2 0.5 mg/d	LDL/HDL cholesterol responses were variable among groups
Taboada *et al.* (39), 2011	10	Low-dose TD E_2 0.0375 mg/d High-dose oral E_2 2.0 mg/d High-dose TD E_2 0.075 mg Oral E_2 0.5, 1, 2 mg/d for 2 weeks each vs TD E_2 0.025, 0.0375, 0.05 mg/d for 2 weeks each	Neither oral nor TD E_2adversely affected rates of protein turnover, lipolysis, and lipid oxidation rates or plasma lipids, fibrinogen, or fasting insulin concentrations
Torres-Santiago *et al.* (3), 2013	40	Oral E_2 2 mg vs TD E_2 0.1 mg	Similar fat-free mass, % fat mass, BMD accrual, lipid oxidation, resting energy expenditure rates No significant changes in lipids, glucose, osteocalcin, hs-CRP
Reinehr *et al.* (60), 2016	490	Oral vs TD (no details available)	Duration and dose of estrogens, route of administration did not correlate significantly to changes of BMI SDS

See Table 3 legend for expansion of other abbreviations.

Abbreviations: BMD, bone mineral density; BMI, body mass index; CE, conjugated estrogen; HDL, high-density lipoprotein; HRT, hormone replacement therapy; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; PTH, parathyroid hormone; WHR, waist-to-hip ratio.

fractures. In girls with TS, TD E_2 administration (25 to 37.5 μg/d) has been reported as better than CEE (0.3 to 0.45 mg/d) for spine bone mineral density (BMD) in one study [0.12 ± 0.01 vs 0.06 ± 0.01 g/cm^2 (mean ± standard error); $P = 0.004$] (22). Findings of a recent study suggest a higher-than-usual oral dose (4 vs 2 mg) during early adulthood improves body composition (increased muscle mass) and increases bone formation markers, which, although BMD was not increased during the study period, in the long run could improve overall bone health (70).

Some adult women with TS prefer combined estrogen and progestin pill options for the sake of convenience (71). Few studies have directly compared TD estrogen regimens with oral regimens in women with premature ovarian insufficiency, including patients with TS. The better-powered studies indicated improved lumbar spine density on a physiological sex steroid–replacement regimen (100 to 150 μg E_2 daily plus 400 mg of vaginal progesterone 2 weeks per month) (48).

On the basis of these studies, the guidelines written by the European Society of Human Reproduction and

Embryology favored TD E_2 for women with premature ovarian failure and commented that OC pills may be appropriate for some women but effects on BMD are less favorable (72–74). More comprehensive long-term studies will be necessary to confirm these results and to examine fracture rates.

Estrogens and uterine growth

Data on the influence of different routes of estrogen therapy on uterine volume are still inconclusive because route, dose, age at onset of treatment, and duration of treatment all influence uterine growth (22, 23, 75–79). However, it is clear the longer the duration of treatment and the higher the dose of estrogen, the better the chances of normalizing uterine size, which is important only if pregnancy options are pursued. One study in 12 girls with TS reported uterine length was significantly greater with TD E_2 treatment (25 to 37.5 μg/d) compared with CEE [0.3 to 0.45 mg/d; 4.13 ± 0.39 vs 1.98 ± 0.39 cm (mean ± standard deviation), respectively; $P = 0.003$] and uterine volume greater [22.2 ± 4.4 vs 4.0 ± 4.4 mL (mean ± standard deviation), respectively; $P = 0.02$] (78). Higher-than-usual doses are often necessary before oocyte donation, where oral doses up to 8 mg have been used for up to 2 years to achieve satisfactory uterine growth (80).

Estrogens/progestin therapy and cardiovascular risk

Although, to our knowledge, there have been no studies in children, or in women with TS, we recommend against CEE use in view of thromboembolic and cardiovascular disease risks reported in postmenopausal women, especially in the first year of treatment using oral estrogen, and in women with existing risk factors like obesity (4, 5, 55, 81, 82).

E_2 replacement therapy, oral or TD, lowers blood pressure (55, 81, 82), although E_2 causes salt and water retention (83). This contrasts with EE-containing contraceptives, which raise blood pressure significantly unless they contain an anti-mineralocorticoid progestin (84).

Recent reports have indicated no increased risk of stroke with progesterone, pregnane derivatives, or nortestosterone derivatives (5, 85). However, norpregnane derivatives were found to increase risk (5). Studies have not been done in TS comparing various progestin options.

Several studies examining both oral E_2 and oral conjugated estrogens vs TD E_2 replacement in the postmenopausal setting have shown increased thromboembolic risk, especially in the first year of treatment in the oral group, that is more pronounced in women with existing risk factors such as obesity (5, 44, 86). Studies directly comparing thromboembolic risk in women with TS have not been done, to our knowledge.

Screening for thromboembolic risk, through measurement of Factor V Leiden and prothrombinase levels, should be done in girls with a personal or family history of VTE; however, routine screening is not recommended, and screening is done only to educate the family about risks, not to postpone estrogen therapy (87). TD estrogen is the preferred treatment in these girls.

Socialization and neurocognitive benefits

Estrogen replacement in girls with TS may improve motor speed and verbal and nonverbal processing time compared with placebo-treated patients with TS (88, 89). In adolescents with TS, oral estrogen therapy improved self-reported self-esteem and psychological well-being over time. At the same time, these patients' parents reported improvement in problem behaviors (90). Data on adults with TS have not been so optimistic. Adults with TS had relative difficulty with measures of spatial and perceptual skills, visual-motor integration, affect recognition, visual memory, attention, and executive function. These deficits were apparent in women with TS despite evidently adequate estrogen treatment (91, 92). Age of onset of puberty influenced sexual experience in one study (93) but not in another (94). A more recent follow-up report suggests that women with TS face more challenges in areas of sexual confidence and self-esteem (95).

The young women with TS who reached normal height and had age-appropriate pubertal development reported normal health-related quality of life; satisfaction with breast development (and height) had a positive influence on several health-related quality of life scales (96). Puberty should be induced at a physiologically appropriate age in patients with TS to optimize self-esteem, social adjustment, and timing of initiation of the patient's sex life. However, one study showed that neither estrogen use nor age of puberty influenced sexual function in patients with TS (94).

Oxandrolone effect on puberty

Oxandrolone is a nonaromatizable weak androgen with direct growth-promoting effects. Low-dose oxandrolone acted synergistically with GH to increase linear growth in several well-controlled studies (48, 97–99). However, oxandrolone may also increase hirsutism and clitoral size slightly, slow pubertal progression modestly (by 1.3 years), and delay menarche in response to estrogen replacement (100). These effects are usually minor and/or transient. Results of one study indicated normal adult breast size is subsequently attained as oxandrolone is discontinued and adult estrogen replacement is instituted (101). Pubic-hair stage was not affected. Therefore, a reasonable suggestion is that treatment with oxandrolone,

0.03 to 0.05 mg/kg/d (maximum, 2.5 mg/d), starting from the age of 10 years onward be considered as adjunctive therapy only in very short girls with TS (100, 102).

Future Research

Only limited data from random controlled trials are available now on girls with TS regarding estrogen treatment options, as discussed. There continues to be a paucity of data from girls and women with TS regarding the regimens discussed in this article and long-term compliance. Questions for future research include the following eight: (1) What is the optimal protocol for pubertal induction, including dose, route, and rate of progression? (2) What are the optimal circulating levels of E_2 during each phase of pubertal induction? (3) What is the optimal dosing, preparation, and timing of progestin-induced uterine bleeding? (4) How long should E_2 treatment be continued in women with TS? (5) What are the optimal method and timing for monitoring bone health in women with TS? (6) What is the optimal regimen to promote uterine growth? (7) If an OC is used for treatment, which are preferable in women with TS? and (8) What is the effect of OC pill placebo days on the hormonal milieu in women with TS?

Conclusion

In summary, we suggest that estrogen replacement should mimic normal physical and social development for timing and progression of puberty, starting between 11 and 12 years of age and increasing over 2 to 3 years. This regimen improves socialization and growth, and optimizes uterine and bone health. Neurocognitive benefits are inconclusive.

When available, low-dose E_2 administered by a systemic route is preferred, and evidence supports its effectiveness and theoretical benefits. When TD E_2 is not available, or compliance is an issue, evidence supports use of oral micronized E_2 or depot E_2 preparations. Only when these forms of E_2 are unavailable should other forms of estrogen be prescribed. Progestin should be added once vaginal bleeding occurs or after 2 years of estrogen treatment. At that time, some women prefer the ease of use of an oral combination of estrogen and progestin. Some preparations are safer than others, and availability varies by country, but, ordinarily, the benefit of good compliance to a chosen regimen outweighs the risks. Treatment is monitored by patient satisfaction and growth and development measures.

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