Estrogen Replacement in Turner Syndrome

Lournaris Torres-Santiago, MD and Nelly Mauras, MD

Nemours Children's Health System, Jacksonville, FL

Primary ovarian failure affects the vast majority of females with Turner Syndrome (TS). Estrogen plays an important role in many body functions including supporting bone health, cardiovascular protection, breast and uterus growth and development, and it influences mood and fat distribution amongst others. If estrogen replacement therapy (ERT) is not initiated and maintained during the reproductive years it can have negative impact in these areas. Hence, adequate estrogen replacement is an essential component in the care of girls and women with TS.

The optimal ERT regimen continues to be an area of study. The proper timing, form, dose and route of estrogen replacement in females with TS are all important considerations.

Type and route of administration

Latest research supports the use a type of estrogen called estradiol as the first choice. It is identical to what the ovaries naturally make, it is the most physiological and levels can be measured through blood work to help determine the best dose for the patient. Conjugated equine estrogen (Premarin®, e.g.) is no longer recommended as a form of ERT as it contains hundreds of estrogen metabolites of different potency which can increase thromboembolic risk.

Estradiol, the purer form of estrogen can be prescribed in injectable, transvaginal, oral or transdermal (patch) forms (Table 1). Research studying the metabolic effects of estradiol compared both oral and transdermal (TD) routes of administration in a group of girls with TS. After 12 months of treatment, despite similar estradiol concentrations in both groups, there were no differences in body composition, lean body mass, adiposity, bone mass accrual or energy expenditure, LH/FSH suppression and lipid concentrations between the groups. IGF-I concentrations (an indirect measure of growth hormone action) trended lower in the transdermal group, but still remained within normal range. Although the blood estradiol levels were comparable in both groups, however, estrone, and estrone sulfate concentrations were considerably higher than normal after oral than transdermal estrogen. Furthermore, using the transdermal route achieved concentrations closer to those of normally menstruating age-matched adolescents. The levels of bio estrogen, estrogen shown to have a biologic effect by activating the estrogen receptor, were substantially higher after oral administration.

Multiple large epidemiologic studies have carefully examined the thromboembolic risk of estrogen and concluded that oral estrogen (all types included) has a higher risk for clotting problems than estrogen via transdermal route. This is believed to be due to the first passage of estrogen via the portal (liver) circulation when given orally, affecting the clotting system. The latest consensus guidelines in the management of estrogen replacement in girls and woman with TS hence suggest that TD estradiol is more physiologic and recommends the use of TD estradiol whenever possible with monthly cycling with oral progesterone.

More recently, we had the opportunity to examine stored sera in the girls that did the study described above and measured a panel of 12 estrogen metabolites after 12 months of oral vs. transdermal estradiol. When estradiol is taken orally, we detected considerable higher levels of metabolites that impair DNA repair ("genotoxic estrogens") compared to levels measured after estradiol was given TD. Although not studied in older women with TS, these metabolites have been implicated in increasing breast cancer risk in post-menopausal women, giving another reason for caution in their use. We recommend at least informed discussion of therapeutic choices before starting estrogen therapy in girls and re-assessment of current programs in adult women.

Timing and dose of Estrogen replacement

It is widely accepted that the goal of ERT is to mimic the normal progression of puberty in girls while maximizing growth potential and minimizing risks. Early treatment with growth hormone (GH) has a better chance of improving growth, especially if started prior to initiating feminization. In instances where GH therapy has been delayed, a delicate balancing of growth promotion and timely feminization are essential and needs to be individualized. Growth hormone can be used simultaneously with estradiol.

In general estradiol should be initiated between 11-12 years of age, assuming levels of LH/FSH (pituitary hormones that increase with the onset of puberty) are high. In cases where maximizing height is a priority, estrogen replacement can be delayed but no later than 14 years of age. Initiation with low doses of estradiol (14 µg daily estradiol, or ½ of the 25µg patch (12.5µg) using patches changed 2x/week) is recommended , dose can be then slowly increased every 6 months over 2-3 years to achieve a typical maximum of 100 µg a day (Table 1). The levels of estradiol can now be measured in the laboratory to assure that one achieves levels comparable to menstruating adolescents. This allows for breast development in a physiologic way. If there is no breakthrough bleeding we can add progesterone, the 2nd hormone produced by the ovary, as oral pills given for 7-10 days a month to allow for menstruation. Oral medroxyprogesterone has been traditionally used, but now micronized progesterone is also available – identical to the natural product and without added pro-clotting risk.

Adolescent girls with Turner syndrome should be feminized at the normal physiologic time, preferably using transdermal estradiol which produces a more physiologic milieu in order to achieve normal levels in plasma.

Length of Therapy

Once adult replacement doses are reached, treatment should continue until the usual age of menopause (~50 years of age), after which risks vs benefits of continuing therapy will need to be individually evaluated.

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.

From Klein, et.al *J Clin Endocrinol Metab*. 2018;103(5):1790-1803.*(with permission)*

References:

Torres-Santiago L, Mericq V, Taboada M, Unanue N, Kelin KO, singh R, Hossain J, Santen R, Ross JL, **Mauras N**. Metabolic effects of oral versus transdermal 17beta-estradiol (E(2)): a randomized clinical trial in girls with Turner syndrome. *J Clin Endocrinol Metab*. 2013;98(7):2716-2724.

Gravholt CH, Andersen NH, Conway GS, Dekkers OM , Geffner ME , Klein KO, Lin AE, **Mauras N** , Quigley CA , Rubin K , Sandberg DE , Sas TCJ , Silberbach M, Söderström-Anttila V , Stochholm K, Alfen-van derVelden JA, Woelfle J , Backeljauw PF for International Turner Syndrome Consensus Group. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol*. 2017;177(3):G1-G70.

Sweetland S, Beral V, Balkwill A, Liu B, Benson VS, Canonico M, Green J, Reeves GK, The Million Women Study C. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. *Journal of thrombosis and haemostasis: JTH*. 2012;10:2277–2286.

Mauras N, Torres-Santiago L, Santen R, Mericq V, Ross JL, Colon-Otero, G, et al. Impact of route of administration on genotoxic oestrogens concentrations using oral vs transdermal oestradiol in girls with Turner syndrome
2019 Jan;90(1):155-161.

Klein KO, Rosenfield R, Santen RJ, Gawlik AM, Backeljauw PF, Gravholt CH, Sas TCJ, **Mauras N.** Estrogen replacement in Turner syndrome: literature review and practical considerations. *J Clin Endocrinol Metab*. 2018;103(5):1790-1803.