

### Dosing Standards for Estrogen

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The hormonal induction of puberty as early as 11 to 12 years of age with low-dose estrogen in hypogonadal girls with TS is safe and effective and does not interfere with linear growth.<sup>1,2</sup> The psychological benefit to undergo age-appropriate pubertal maturation is supported by reports of increased quality of life and psychological well-being in adults with TS who did not experience delayed induction of puberty and late menarche.<sup>3,4</sup>

Exogenous hormone therapy is aimed to most closely mimic physiologic puberty and is preferably coordinated with the final phase of growth hormone therapy. Evidence is increasing that transdermal micronized estradiol is the most physiological form and route of estrogen therapy commercially available. In a recent study, transdermal estradiol therapy resulted in levels of estradiol, estrone, and bioestrogen metabolites closer to normal and with a greater suppression of LH and FSH levels than following oral estradiol replacement.<sup>5,6</sup> For patients who are unable to tolerate estradiol patch therapy or prefer to use pills, the use of low dose oral micronized estradiol provides a reasonable therapeutic alternative, with an initial dose of 0.25 mg daily.

The overall approach is to increase the estrogen dose gradually over 3 to 3 ½ years and to use growth, bone maturation, hormone levels, degree of feminization, patient satisfaction, bleeding pattern, and side effects as a guide. To ensure a healthy endometrium, a progestin should be introduced approximately 2 ½ years after starting estrogen or earlier if breakthrough bleeding occurs. For the physician caring for young adult women with TS, from both the physiological and safety perspectives, the continued use of transdermal estradiol with a cyclical progestin once puberty is complete makes sense. This daily regimen is relatively complex and may be expensive, if the estradiol patches are not covered by insurance. Compliance may not be sufficient to preserve bone health. Oral estradiol at a dose of 1-2 mg a day cycled with a progestin is less costly and some patients find it easier to take a daily pill than change patches once to twice weekly. The oral contraceptive pill is more than adequate for bone health, is less expensive, convenient to use and rarely is associated with intra-cycle bleeding.<sup>7</sup> The adverse publicity to chronic estrogen use stemming from the WHI study can be addressed by providing a simple explanation of how the findings do not apply to younger women going through menopause and younger hypogonadal women.

The specifics of low dose regimens to induce puberty in adolescents with TS continue to be explored and evaluated.<sup>8</sup> One approach adopted by many, has been the use of fractionated or partial estradiol patches to achieve a very low dose at the start of pubertal induction. An alternative best practice soon to be assessed in a multicenter Quality Initiative being sponsored by the Pediatric Endocrine Society and open to all its members for participation, enables the initiation of puberty with the application of an entire 25 mcg estradiol patch for one week,

monthly and then titrating the dose gradually by initially increasing the duration of patch usage and subsequently the patch dose.

- <sup>1</sup>Rosenfield RL, Devine N, Hunold JJ, Mauras N, Moshang T, Jr., Root AW 2005 Salutary effects of combining early very low-dose systemic estradiol with growth hormone therapy in girls with Turner syndrome. *J Clin Endocrinol Metab* 90:6424-6430
- <sup>2</sup>Ross JL, Quigley CA, Cao D, Feuillan P, Kowal K, Chipman JJ, Cutler GB, Jr. 2011 Growth hormone plus childhood low-dose estrogen in Turner's syndrome. *N Engl J Med* 364:1230-1242
- <sup>3</sup>Carel JC, Ecosse E, Bastie-Sigeac I, et al. Quality of life determinants in young women with Turner's syndrome after growth hormone treatment: results of stature population-based cohort study. *J Clin Endocrinol Metab.* 2005; 90:1992-1997.
- <sup>4</sup>Boman UW, Bryman I, Moller A. Psychological well-being in women with Turner syndrome: somatic and social correlates. *J Psychosom Obstet Gynaecol.* 2004; 25(3-4):211-219.
- <sup>5</sup>Torres-Santiago L, Mericq V, Taboada M, Unanue N, Klein K, Singh R, Hossain J, Santen R, Ross J, Mauras N 2013 Metabolic effects of oral vs. transdermal 17beta estradiol (E2): a randomized clinical trial in girls with Turner Syndrome. *J Clin Endocrinol Metab* 98:2716-2724
- <sup>6</sup>Taboada M, Santen R, Lima J, Hossain J, Singh R, Klein KO, Mauras N 2011 Pharmacokinetics and pharmacodynamics of oral and transdermal 17beta estradiol in girls with Turner syndrome. *J Clin Endocrinol Metab* 96:3502-3510
- <sup>7</sup>van Pareren YK, de Muinck Keizer-Schrama SM, Stijnen T, Sas TC, Jansen M, Otten BJ, Hoorweg-Nijman JJ, Vulmsa T, Stokvis-Brantsma WH, Rouwe CW, Reeser HM, Gerver WJ, Gosen JJ, Rongen-Westerlaken C, Drop SL 2003 Final height in girls with turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *J Clin Endocrinol Metab* 88:1119-1125
- <sup>8</sup>Bondy CA, for the Turner Syndrome Consensus Study Group 2007 Care of girls and women with Turner syndrome: a guideline of the Turner syndrome study group. *J Clin Endocrinol Metab* 92:10-25