Sex Hormone Replacement in Turner Syndrome

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spontaneous puberty in TS

- **Approximately one-third of girls with TS have spontaneous breast development that may progress to menarche, often in girls with mosaicism.**

- **Spontaneous menarche presents in few (6%–9%) 45,X TS.**
- **mosaic TS (45,X/46,XX), presents with spontaneous menarche in 20% to 40% of the cases.**
- **If gonadotropin concentrations are normal for age, observation for spontaneous puberty is appropriate, with future replacement therapy if gonadal failure occurs.**

Sex Hormone Replacement Therapy is necessary to:

1) induce puberty, growth of the uterus, to maintain secondary sex characteristics and sexual function
2) growth of the hight
3) appropriate peak bone mass (increased BMD)
4) lean body mass, motor speed
5) Improve the liver function and metabolic profile
6) Improve the cardiovascular system (including blood pressure)
7) neurocognitive function and positive influence on body composition
8) play a role in memory and mood and verbal and nonverbal processing time, self-esteem and improvement in problem behaviors.

Symptoms of oestrogen deficiency

1) increased risk for stroke, ischaemic heart disease and early death
2) changes in mood (depression and poor concentration)
3) reduction in energy
4) skin elasticity
5) breast size and vaginal dryness
6) flushing and this can often feel like intolerance to heat
7) osteoporosis

Best time to start SHRT

- 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.
- Low anti-Mu¨llerian hormone (AMH)levels and undetectable inhibin B levels have been reported to predict ovarian failure in TS.
- AMH in 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.
- Delay of pubertal initiation beyond 14-15 years were of greater concern.

Pubertal development after SHRT

- Estrogenization of the vaginal mucosa lags behind changes in serum E2 TD by about 1 week.
- Incremental dose increases at ;6-month intervals can mimic the normal pubertal tempo until adult dosing is reached over 2 to 3 years.
- onset of breast buds within 6 months in most girls.
- Pubertal stage 4 breasts in an average of 2.25 years.
- Menstruation will be often until 24 months.

Estrogens and linear growth

- If potential for taller stature is still possible, girls may take lower estrogen doses for a longer time.
- Very low doses of EE and E2 do not interfere with growth response to GH therapy when started at≤12 years of age.
- Early treatment with ultralow-dose estrogen may improve growth.
- no change in IGF-1 concentration after oral or TD therapy.
- bone age advanced less when using TD E2 than oral E2 At the same time, growth velocity was greater when using TD E2 than oral E2 at 1 year suggesting overall better growth.

Estrogens and linear growth

- 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.
- When height is a greater concern, often GH treatment can be initiated before low-dose E2; however, we recommend that E2 not be delayed past 14 years of age.
- If girls are already older at initiation, the duration until adult dosing may be shortened.
- When feminization is a greater concern, GH and E2 can be started simultaneously.

Estrogens and bone density

- **Delaying estrogen replacement is deleterious to bone health.**

- **TD E2 administration (25 to37.5 mcg/d) has been reported as better than CEE (0.3 to 0.45 mg/d) for spine bone mineral density (BMD) in one study.**

the guidelines written by the European Society of Human Reproduction and Embryology 2020

Low dose Androgen therapy plus Estrogen

1) increased BMD
2) lean body mass and decreased fat mass
3) skeletal muscle power
4) improved quality of life and psychosocial well-being , stress coping , cognition
5) sexual desire and libido.
6) decreased total cholesterol
7) decreased blood pressure.

- decreased insulin sensitivity
- decreased total HDL cholesterol

- Hormone Replacement Therapy to Treat Turner Syndrome and Up to date (brief 2008- 2020)

oxandrolone

- **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.**

- **Normal development of adult breast size after discontinues oxandrolone and during ERT.**

- **Pubic-hair stage was not affected.**

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	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

Transdermal estrogen patches and gels

- enter directly into the bloodstream, avoid first-pass hepatic metabolism so Current studies suggest the body utilizes estrogen is choice:

1) decrease the risk of blood clots
2) improve blood pressure control
3) result in better bone mass
4) improve the effectiveness of growth hormone
5) ideal in women with liver disease or hypertriglyceridemia.
6) bone age advanced less when using TD E2 than oral E2

- 10% of women develop skin reactions

A Pubertal Transdermal Estradiol Replacement Regimen Beginning at 11 Years of Age(sperling2020)

Age	Estradiol Dose
0–6 months	14 mcg, day 1–7 each month
6–12 months	14 mcg, day 1–14 each month
1–1.5 years	14 mcg, day 1–21 each month
1.5–2 years	25 mcg, day 1–21 each month
2–2.5 years	37.5 mcg, day 1–21 each month
2.5–3 years	28-day cycle: 50 mcg day 1–21 and Prometrium® 100 mg[b] day 12–21 every 28 days OR Continuous: 50 mcg day 1–14, then Combipatch® (50 mcg estradiol/0.14 mg norethindrone) day 16–28 every 28 days
3–3.5.years	28–day cycle: 75 mcg day 1–21 and Prometrium® 100 mg day 12–21 every 28 days OR Continuous: 75 mcg day 1–14 then Combipatch® (50 mcg estradiol/norethindrone) day 16–28 every 28 days
3.5–4 years	28-day cycle: 100 mcg day 1–21 and Prometrium® 100mg day 12–21 every 28 days OR 100 mcg day 1–14 then Combipatch® (50 mcg estradiol/norethindrone) day 16–28 every 28 days
>4.0 years	Continue regimen or offer oral contraceptive pill

[a]In children ≥13 years old, consider starting with 25 mcg for 2–3 weeks monthly and increasing the dose at shorter intervals (e.g., 3 months).
[b]If inadequate bleeding, increase Prometrium to 200 mg day 12–21 or change to Combipatch 50 mcg estradiol/0.25mg norethindrone.

Practical Considerations(Patch & Gel)

- Patches with a matrix design can be easily cut, whereas patches with a reservoir technology should not be cut.
- the Pediatric Endocrine Society, which recommended initiating cyclic
- initiate puberty with low-dose TD E2, 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.
- increase every 6 to 12 months based on response and growth potential.

- Some European countries have approved an E2 gel, 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

Oral estrogen

- oral administration leads to a more unphysiological pattern of 17β-oestradiol, oestrone and oestrone sulfate.

- No significant differences between receiving TD vs oral estrogen treatment:
- glucose, insulin tolerance, fasting insulin concentration
- protein turnover and lipolysis
- osteocalcin or highly sensitive C-reactive protein
- body mass index or waist-to-hip ratio
- Oral regimen begins with 5 mcg/kg micronized estradiol (Estrace®, 0.25 mg for a 50 kg girl) daily; the adult replacement dose is 1 to 2 mg/day.

The higher dose of estrogen (4 vs 2 mg) during early adulthood

- the better the chances of normalizing uterine size,for pregnancy(before oocyte donation, where oral doses up to 8 mg have been used for up to 2 years)
- improves body composition(increased muscle mass)
- increases bone formation markers, improve overall bone health and lumbar spine density .
- normalization of liver function

Depot E2 route

- depot E2 monthly injections at very low doses stimulated normal pubertal growth and development in conjunction with GH treatment.
- it is less attractive because of the pain of injection.
- IM depot estradiol in a starting dose of 0.2 mg/month will usually induce breast budding; the dose should be increased by 0.2 mg every 6 months.
- A midpubertal dose of 1.0 to 1.5 mg monthly, which is half the adult replacement dose, typically induces menarche within 1 year.

Progestins

- First-generation OCs contain 50 mcg of the estrogen mestranol and the progestogen norethynodrel
- later generation pills use 20 to 35 mcg of EE as the estrogen.
- Second-generation progestogens include norethindrone ; its acetate, ethynodiol diacetate; and levonorgestrel.
- Third-generation progestogens include desogestrel, norgestimate, and gestodene.
- Fourth-generation pills include drospirenone.
- norpregnane derivatives were found to increase risk of Stroke.

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

Progestins

- decrease the risk of endometrial hyperplasia and endometrial carcinoma
- 19-nor-progesterone derivatives are associated with androgenic action
- medroxyprogesterone acetate with glucocorticoid-agonistic action
- drospirenone with antiandrogenic and anti-mineralocorticoid actions.

Progestins

- Must be added after 2 years of E2 treatment or when bleeding begins to occur.
- 100 mg of micronized progesterone (Prometrium®) at bedtime for 7 to 14 days during the second to third week of estrogen therapy
- Or medroxyprogesterone acetate (5–10 mg/day)
- Or norethindrone acetate (5 mg/day).

Intrauterine devices containing a progestin

- **block endometrial hyperplasia and unwanted bleeding**

- **If bleeding irregularities occur: intrauterine progestin coated device can be used together with either continuous oral or TD E2.**

Common Progestin and Estrogen/Progestin Combination Replacement Options

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		

contraceptive pills

- Most patients prefer to switch to combined oral contraceptive pills (OCP).
- Ocs for HRT is generally not recommended in young women with Turner syndrome
- The pills containing the lowest dose of estrogen.
- currently available in combination contraceptive pills in the United States contain 20 mcg (Mircette®) to 30 mcg (Yasmin®) ethinyl estradiol.
- All OCs increase the risk of venothrombotic episodes (VTEs).
- A recent guideline 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, Micronized progesterone is associated with a lesser risk.

Combined HRT in TS

- **combined sequential regimens :estrogen for 21 to 25 days and the progestin for only 10 to 14 days.**
- **The combined sequential regimens are associated with menstruation and are preferred in younger women**
- **The combined continuous regimens prevent uterine bleeding, an attractive factor for older women.**

Monitoring Treatment

- **Routine monitoring of serum LH or FSH levels is not recommended**
- **E2 measurement using a sensitive assay (LC/MS) allows dose titration**
- **Clinical assessment, patient satisfaction, patient age, and residual growth potential are the primary determinants for dose increase.**

Adult Estrogen Therapy

- **Adult TD replacement doses of 50 to 150 µg/d**
- **oral replacement doses of 2 to 4 mg of E2**
- **Oral progestin for 10 days per month or continuous progestin regimens are suggested**
- **Selective SHRT For the adult TS:**
- **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**
- **Close collaboration with a gynecologist**

Duration

- **Treatment should continue until the time of usual menopause, around age 51 to 53 years.**
- **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.**

summary

- Treatment should begin at age 11 to 12 years, with dose increases over 2 to 3 years.
- Delaying estrogen replacement may be deleterious to bone and uterine health.
- Initiation with low-dose estradiol (E2) is crucial to preserve growth potential.
- Evidence supports the effectiveness of starting pubertal estrogen replacement with low-dose transdermal E2.
- When transdermal E2 is unavailable or the patient prefers, evidence supports use of oral micronized E2 or an intramuscular preparation.
- Only when these are unavailable should ethinyl E2 be prescribed.
- We recommend against the use of conjugated estrogens.
- For adults who have undergone pubertal development, we suggest transdermal estrogen and oral progestin

Transition of care for young adult patients with Turner syndrome

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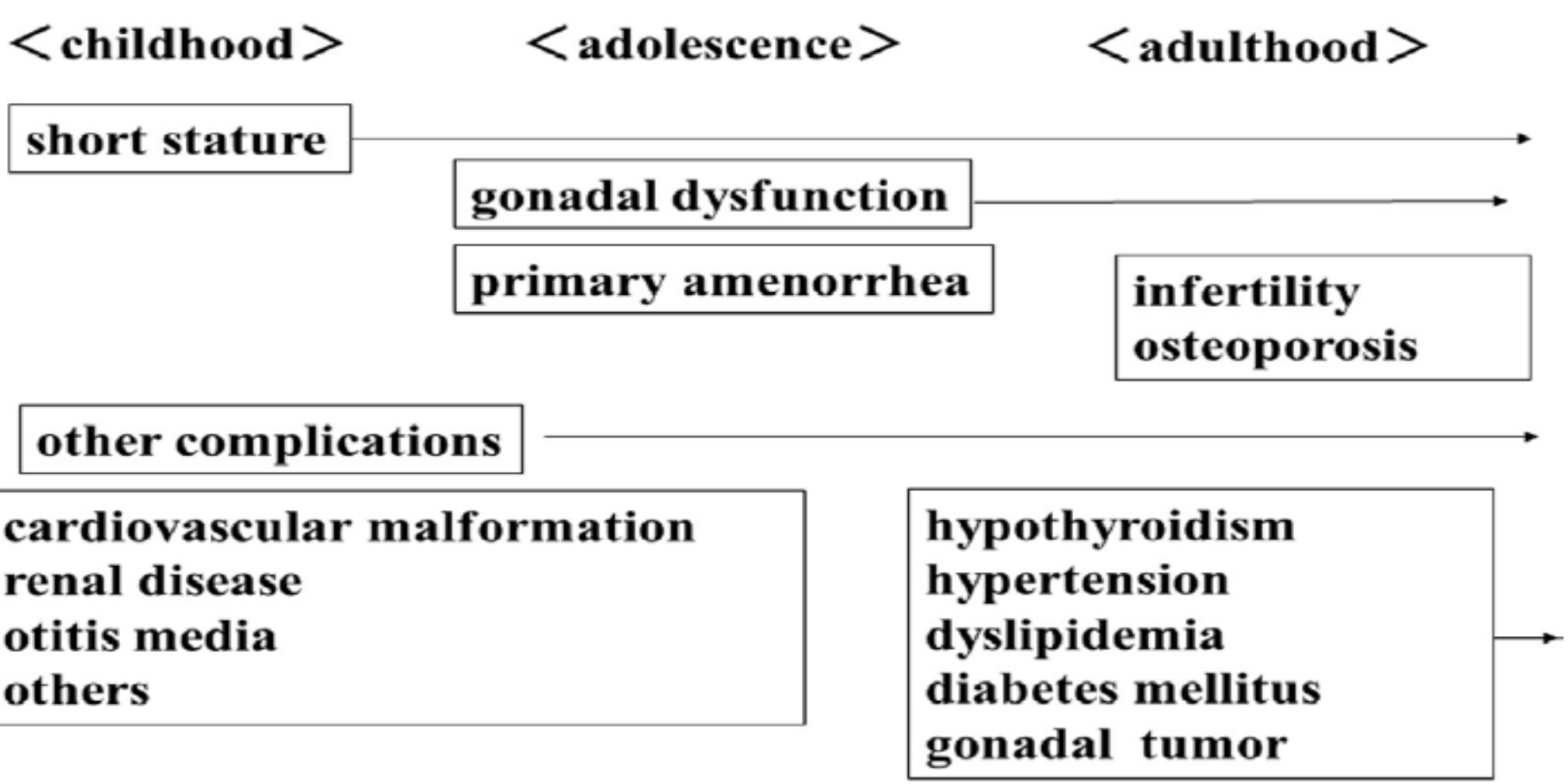
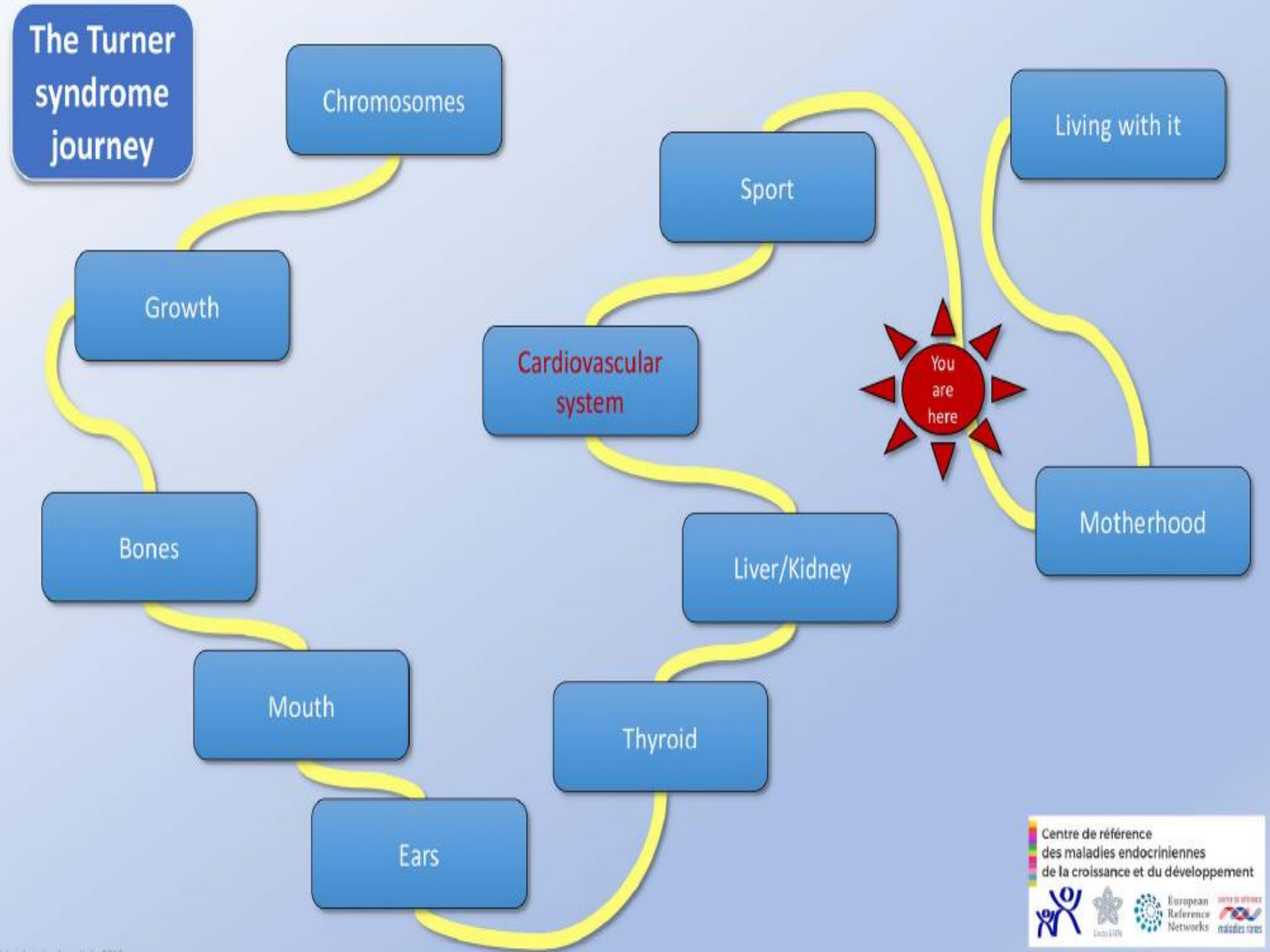
Transition of Women with Turner Syndrome from pediatrics to Adult




The Turner syndrome journey
Chromosomes
Growth
Bones
Mouth
Ears
Thyroid
Liver/Kidney
Cardiovascular system
Sport
You are here
Living with it
Motherhood
Centre de référence
des maladies endocriniennes
de la croissance et du développement
European Reference Networks

Multidisciplinary approaches

- Hormone Replacement Therapy
- Cardiovascular disease, hypertension
- Autoimmune disorders (Hypothyroidism, Celiac Disease)
- Metabolic Syndrome (Diabetes, Liver function, over weight)
- Otorhinolarngologic aspect
- Metabolic bone disease
- Exercise/Fitness/Weight control
- Learning Disabilities
- sexuality and quality of life
- Fertility and pregnancy (more than 10–12 oocytes are necessary)
- Socioeconomic factors(depression, anxiety, and low-self esteemcollege, jobs, partnerships, reduced motherhood and earlier retirement)

Screening for thromboembolic risk

- routine screening is not recommended
- Screening for thromboembolic risk (Factor V Leiden and prothrombinase levels):

girls with a personal or family history of VTE

- TD estrogen is the preferred treatment in these girls.
- Overweight and obesity is a risk factor for thromboembolism when using estrogen, hypertension, diabetes, and other components of the "metabolic syndrome"

Diabetes

- There is a 10 to 11-fold increased risk of T1D with an observed frequency of 1% in adult women with Turner syndrome
- More than 50% of women with Turner syndrome have an abnormality in glucose homeostasis including insulin resistance, impaired glucose tolerance, and T2D.
- T2D in adult women with Turner syndrome is three to fivefold higher than controls
- Incidence of IGT increase from 10% of children to 16% in adolescents and 41% in adults with Turner syndrome
- no negative influence of GH plus estrogen therapy on β cell function

Mortality

- The overall mortality is increased threefold
- Mortality is raised four to fivefold in women with 45,X karyotype, but only twofold in 45,X/46,XX mosaicsm.
- there is a 13–15 years reduction in lifespan.
- Almost 50% of the excess mortality is caused by cardiovascular disease.
- Endocrine disorders such as diabetes also contribute to the increased mortality.
- increased risk of death from neurological conditions: epilepsy(particularly
- under age 15 years)
- liver disease and colitis(15-44 y)
- physiologic hormone replacement might reduce morbidity and mortality
- There is no higher rate of cancer in TS patients from population.