Sindrome di Turner dall'infanzia all'età adulta

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Bambino Gesù
OSPEDALE PEDIATRICO

sima
SOCIETÀ ITALIANA di MEDICINA dell'ADOLESCENZA

UNIVERSITA' DEGLI STUDI DI ROMA
TorVergata

Sindrome di Turner

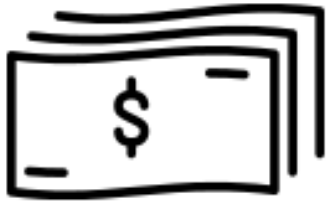
Prevalenza Stimata e costi

~1/2500 live female births

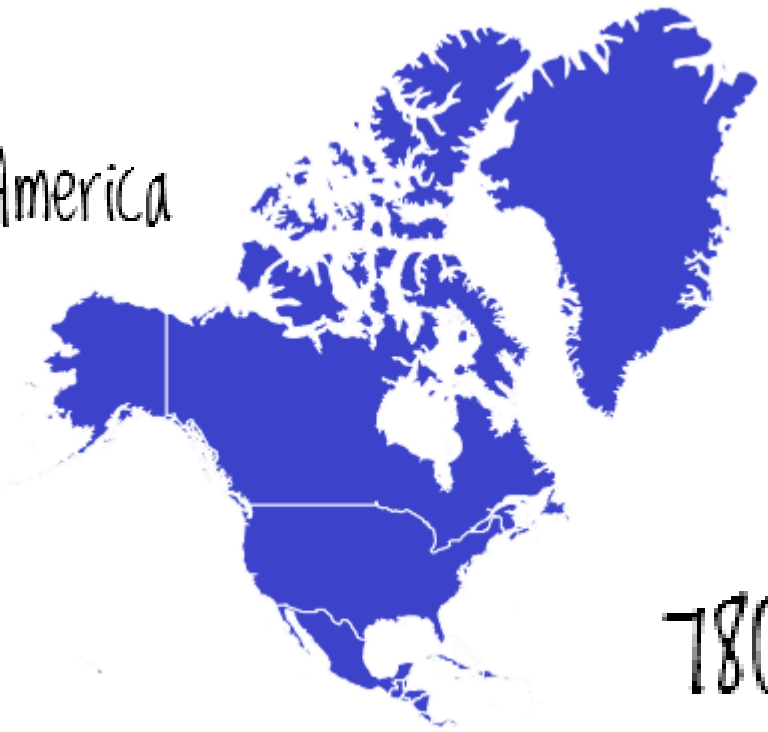
125500

Europe

=



United States of America



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Sindrome di Turner

Breve panoramica I

«The diagnosis of TS requires the presence of characteristic physical features in phenotypic females, coupled with complete or partial absence of the second sex chromosome, with or without cell line mosaicism».

Turner HH 1938 A syndrome of infantilism, congenital webbed neck, and cubitus valgus. Endocrinology 23:566–574
Ferguson-SmithMA1965 Karyotype-phenotype correlations in gonadal dysgenesis and their bearing on the pathogenesis of malformations. J Med Genet. 2:142–155

- 1:2500 nati vivi di sesso femminile (+ undiagnosed cases);
- Cariotipo:

Turner syndrome karyotypes

Karyotype	Percentage of Turner syndrome cases (%)
45,X	45
46,X,i(X)(q10), with or without 45,X	15-18
46,X,+mar or +r, with or without 45,X	7-16
45,X/46,XX or 45,X/47,XXX	7-16
46,X,del(Xp), with or without 45,X	2-5
46,XY or 46,X,del(Y) or 46,X,r(Y), with 45,X	6-11
Others	2-8

Fig.1 *Cariotipi possibili e relative frequenze nella sindrome di Turner. Wolff DJ, Van Dyke DL, Powell CM. Laboratory guideline for Turner syndrome. Genet Med 2010; 12:52.*

Sindrome di Turner

Diagnosi

- Prenatale
  - Incidentale (villocentesi, amniocentesi)
  - Sospetto di Turner per caratteristiche ecografiche
- Post-natale

  Linfedema, bassa statura, amenorrea primaria, caratteri fenotipici Turner

- Analisi del cariotipo
  - Almeno 30 cellule mononucleate in metafase
  - Fibroblasti della pelle
- Pirosequenziamento
- Ricerca di materiale cromosomico Y
- Ritardo diagnostico (mild phenotype); casi NON diagnosticati (30%)

Sindrome di Turner

Breve panoramica II

- Caratteristiche fenotipiche fetali
  - Idrope di tronco e arti
  - Igroma cistico
  - Effusione pleurica
  - Ascite
  - Incremento traslucenza nucale

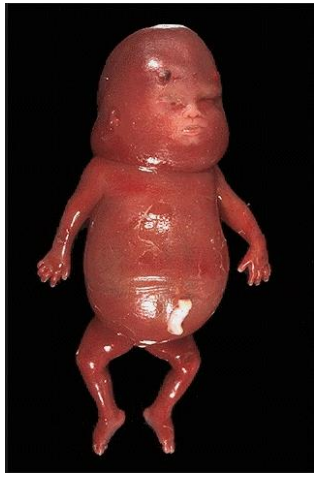


***Fig.2**. Igroma cistico e idrope fetale.*

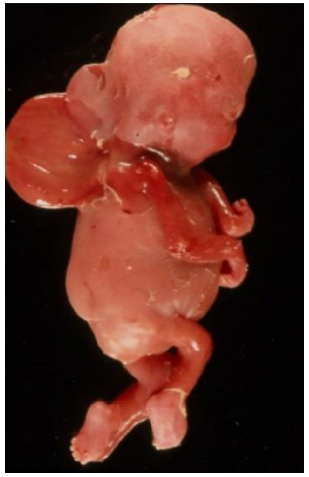
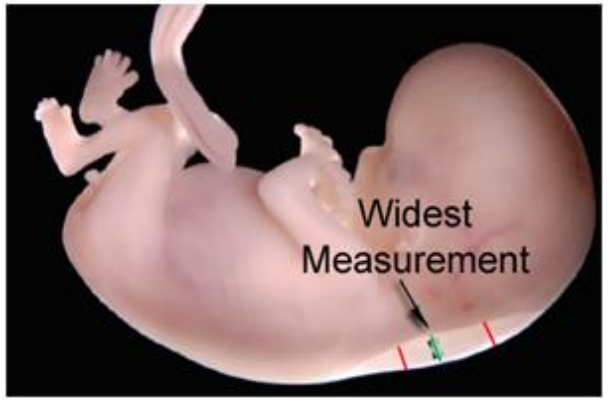
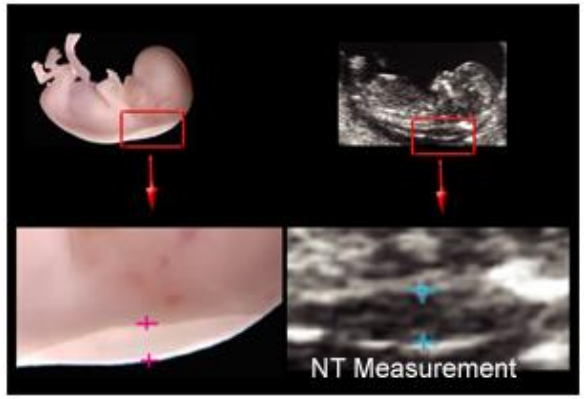
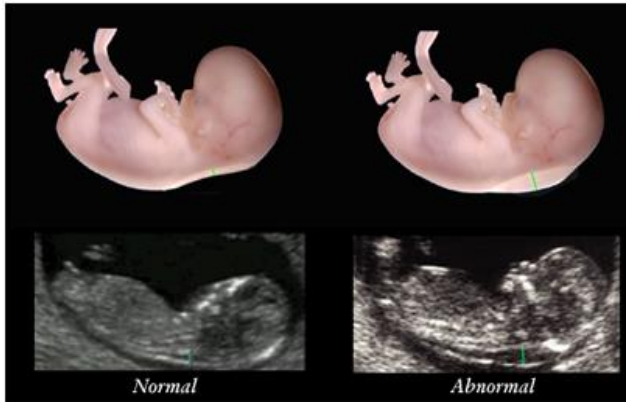


***Fig.3**. Igroma cistico.*







***Figg.4-6.** Misurazione della traslucenza nucale e confronto tra reperto normale e anomalo. http://www.fetal.com/NT%20Screening/02%20NT%20Imaging.html*

Sindrome di Turner

Breve panoramica III

- Caratteristiche fenotipiche post-natali
  - Bassa statura 95-100% -SHOX gene-
  - Infertilità 95%
  - POF 90%
  - Disgenesia gonadica 85-90%
  - Anomalie correlate all'ipoplasia linfatica 20-40%
  - Micrognazia 60%, malocclusione →75%
  - Malformazioni a carico del s. cardiovascolare →50%
  - Cubito valgo 50%
  - Cifosi 50%, scoliosi 10-20%
  - Capezzoli distanziati 30-35%
  - Tiroidite autoimmune 15-30%
  - Anomalie renali e reno-vascolari >30%
  - Anomalie funzionali organi di senso
  - …

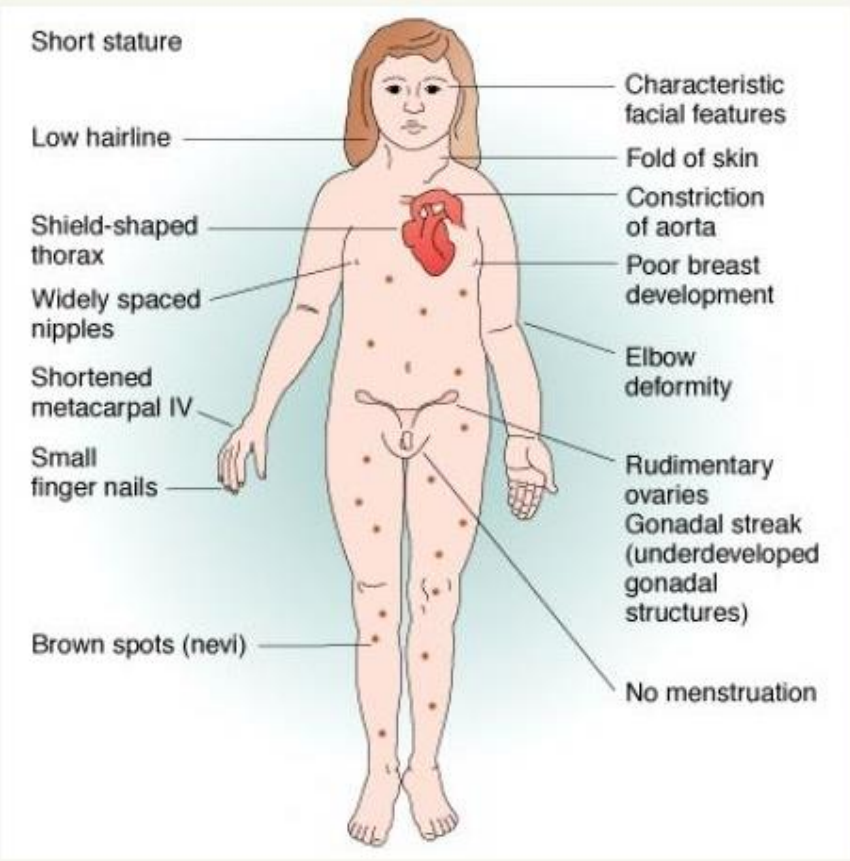


Fig.7. *Caratteristiche fenotipiche comuni nella Sindrome di Turner.* https://pedclerk.bsd.uchicago.edu/page/turner-syndrome

Fonte: https://www.uptodate.com/contents/image?imageKey=ENDO%2F60006&topicKey=ENDO%2F7391&source=outline_link&search=turner&selectedTitle=1~150

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting

www.eje-online.org
DOI: 10.1530/EJE-17-0430

Table 1 Type and frequency of chromosome abnormalities in Turner syndrome.

Karyotype	%	Description
45,X	40–50	Monosomy X
45,X/46,XX	15–25	
45,X/47,XXX; 45,X/46,XX/47,XXX	3	Mosaicism with 'Triple X'
45,X/46,XY	10–12	Mixed gonadal dysgenesis
46,XX, del(p22.3); 46,X,r(X)/46,XX		Deletion Xp22.3 Ring X chromosome
46,X i(Xq); 46,X,idic(Xp)	(10%)	Isochromosome Xq; isodicentric Xp
X-autosome translocation, unbalanced	Rare	Various
46,XX,del(q24)		Not TS; premature ovarian failure
46,X,idic(X)(q24)		Not TS; isodicentric Xq24

Condizione clinica con interessamento di più organi/apparati

- Apparato cardiovascolare
- Fegato, ricambio glicidico
- Apparato urinario
- Osso
- Autoimmunità
- Cute
- Apparato uditivo

R 1.5. We recommend gonadectomy in all female individuals with Y chromosome material identified on standard karyotyping (⊕⊕◯◯).

Clinical Practice Guideline | C H Gravholt and others | Turner syndrome clinical practice guideline | 177:3 | G1–G70

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting

British Medical Bulletin, 2015, **113**:45–58
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Turner syndrome–issues to consider for transition to adulthood

Laura Lucaccioni[†], Sze Choong Wong[†], Arlene Smyth[‡], Helen Lyall[§], Anna Dominiczak[**], S. Faisal Ahmed[†], and Avril Mason[†,*]

Review | A Gawlik and E Malecka-Tendera | Turner's syndrome during transition | 170:2 | **R57**–R74

TRANSITION IN ENDOCRINOLOGY

Treatment of Turner's syndrome during transition

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Table 5 Suggested assessment in Turner syndrome prior to pubertal induction and transition

	Childhood	Young person—prior to transition
Auxology	Height, weight Pubertal assessment (from 10 years)	Height/weight Pubertal assessment
Growth hormone monitoring	IGF1 and bone age (if on growth hormone therapy) Thyroid function	Thyroid function
Ovarian reserve	FSH, AMH (at diagnosis) Pelvic ultrasound (prior to pubertal induction)	Pelvic ultrasound Counsel young person and family regarding fertility
Cardiovascular	Cardiac assessment and echocardiogram (diagnosis) Blood pressure (every clinic)	Cardiac assessment, echocardiogram ± MRI Blood pressure
Bone	Examine for scoliosis (before commencing growth hormone and annually)	DXA scan
Autoimmune	Thyroid peroxidase antibody (diagnosis) Thyroid function (diagnosis and then annually if on growth hormone) Coeliac screen (12 years)	Thyroid function Coeliac screen
ENT	Hearing test (diagnosis) ENT referral if appropriate	Hearing test
Renal	Renal ultrasound (diagnosis) Urine culture if any renal abnormalities	–
Liver	Liver function (12 years)	Liver function
Metabolic	–	Fasting glucose, lipids, HbA1C
Psychosocial	Review school performance	Vocational advice

Table 1 Turner's syndrome – natural history of associated medical problems.

	Birth/infancy	Preschool	School	Adolescence	Young adulthood
Short stature		→	→	Consequences of GH therapy	Consequences of GH therapy
Cardiovascular disorders	→	→	→	→ Hypertension	→ Hypertension
Otolaryngology problems		→ Otitis media/CHL	→ Otitis media/CHL		→ SNHL
Delayed puberty/ovarian failure				→ HRT	→ HRT/infertility
Renal anomalies	→	→	→	→	→
Obesity/metabolic disorders			→	→	→
Autoimmune diseases				→	→
Behavioural difficulties		→	→ +Specific learning difficulties	→ +Specific learning difficulties	→
Visuo-spatial difficulties					→
Osteoporosis					→
Other features of TS	→	→	→	→	→

→, present; CHL, conductive hearing loss; SNHL, sensorineural hearing loss; HRT, hormonal replacement therapy.

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Sindrome di Turner

Terapia, cenni

- GH (early start and dose), eventualmente associato a:

  Oxandrolone , OPPURE

  Induzione tardiva della pubertà

- Terapia Ormonale

- Estrogeni
- Estro-progestinici

- Trattamento delle condizioni associate (tiroidite, ipertensione, DM, …)

Table 2 Growth therapy, determinants of therapy effectiveness, consequences and side effects.

References	No. total/GH	Duration of GH treatment (s.d.)	Mean/range GH dose (mg/kg per week)	Gain in FH (cm)	FH (s.d.) (cm)	Consequences/side effects of growth therapy
(4)	83/62					
(5)	180	5.8 (2.4)	0.26	–	150.3 (6.0)	–
(7)	33	Ongoing	0.26			
(14)[a,b]	104/61	5.7 (1.6)	0.30	7.2	149.0 (6.4)	No difference between GH-treated and untreated in glucose level, HbA1c, T_4, TSH. GH-treated: higher incidence in surgical procedures, otitis media, joint disorders, sinusitis; lower incidence – goiter
(15)	708	5.0 (2.2)	0.26	8.5	149.9 (6.1)	–
(16)	212	Ongoing		–		–
(17)[b]	49/21	4.0 (1.5)	0.33		150 (5.1)	No side effects
(18)	186	5.2 (2.6)	0.33		151.7	–
(19)	242					–
(20)[b]	119/60		0.33		151.0 (6.1)	No side effects
(21)[a,b]	149/67	6.5	0.30	5.0	144.8^{GH} 146.8^{GH+E}	–
(22)	987	–	0.28	–	$151.0^{NAH(median)}$	–
(23)	77	6.3	0.27	6.1	153.5	–
(24)	382	–	0.36	–	–	–
(25)[a,b]	76	Ongoing	0.35	–	–	Ox addition – slowed breast development and delayed the menarche, no influence on bone mineral density
(26)	463		0.29		151.6	

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References	No. total/GH	Duration of GH treatment (s.d.)	Mean/range GH dose (mg/kg per week)	Gain in FH (cm)	FH (s.d.) (cm)	Consequences/side effects of growth therapy
(27)[a,b]	92	–	0.35	–	151.4 (6.7)	
(28)[a,b]	82		0.32		155.6–156.7	More frequent virilisation in higher dose of Ox (0.06 mg/kg per day) compared with lower does (0.03 mg/kg per day)
(29)	62	Ongoing	0.33			
(30)	?	–	–	4.28	147.3	–
(31)	158	5.6 (2.3)	0.31	–	151.4	
(32)	54/35	–	0.30	7.3	–	–
(33)[b]	43	Ongoing	0.29	–	–	–
(34)	175/115	Ongoing	0.3–0.33	–	–	–
(35)	120				?	
(36)[b]	46/23	5.0 (2.1)	0.30–0.38		145.2 (10.9)	No effect on bone density and fracture risk
(37)[b]	67/39	4.2 (3.2)	0.21–0.35	–	–	GH increases muscle mass, reduces adiposity
(38)[b]	102/76	Ongoing	0.21–0.35	–	–	In GH group better glucose tolerance and lower abdominal adiposity vs untreated TS
(39)	?		?		?	History of GH use: lower total body and abdominal fat mass
(40, 41)[b]	82/30	3.7 (1.5)	0.42	–	146.2	No influence on body composition. No influence on body proportions, except for hand length
(42)[a,b]	112		0.32			Ox addition (0.06 mg/kg per day): increases sitting height, reduces subcutaneous fat mass. Ox in lower dose (0.03 mg/kg per day): decreases biiliacal distance. Both Ox doses: increase muscle mass
(43)	46	6.3 (2.5)	0.33		156.0 (5.5)	GH reduces insulin sensitivity, GH cessation – insulin sensitivity returns to pre-therapy values. Oestrogens worsen the indices of insulin sensitivity
(44)	39	8.7 (2.0)	0.31–0.63		162 (6.9)	Metabolic consequences 5 years after GH therapy: higher total cholesterol, higher HDL, insulin sensitivity lower, β-cell function and fasting insulin remained higher, atherogenic index – constant
(45)	86/67	4.4	0.35	–	145.7 (9.4)	GH has no effect on cardiac dimension
(46)	33/21	–	0.30	–	148.9	No benefits and adverse effects on HRQOL

References	No. total/GH	Duration of GH treatment (S.D.)	Mean/range GH dose (mg/kg per week)	Gain in FH (cm)	FH (S.D.) (cm)	Consequences/side effects of growth therapy
(47)[b]	111/58	–	0.23	–	154.7 (5.0)	GH: except for less pain, no impact on QOL
(48)	568	4.8 (2.2)	0.26		150.9 (5.6)	GH: no benefits and adverse effects on QOL
(49)	117	4.0–9.4	0.23–0.47	–	151–158	No negative effect of GH and androgen treatment on voice function, it reduced the risk of voice and articulation problems in adulthood
(50)	5220	–	–	–	–	GH increases risk of intracranial hypertension, scoliosis, slipped capital femoral epiphysis. The risk for events associated with TS in group with GH vs without GH – unknown

TRANSITION IN ENDOCRINOLOGY

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Table 4 Hormone replacement therapy in Turner's syndrome: suggestions (2).

Age	Suggestions	Route	Dose
10–11	Puberty assessment/FSH/AMH	t/d	Decision about low-dose E_2 (?)
12–13	No puberty/elevated FSH/check AMH	t/d	6.25 μg/day
		p.o.	0.25 mg/day micronised E_2
		i.m.	0.2–0.4 mg/month depo E_2
12.5–15	Gradual increase in E_2 dose over 2 years to adult dose	t/d	Adult: 100–200 μg
		p.o.	Adult: 2–4 mg micronised E_2
			Adult: 20 μg EE_2
			Adult: 1.25–2.5 mg CEE
14–16	After 2 years or when breakthrough bleeding occurs – add cyclic progesterone	p.o.	Adult: 200 mg/day (cyclic)
14–30	Full dose of oestrogen	t/d	Adult: 100–200 μg
		p.o.	Adult: 2–4 mg micronised E_2
			Adult: 20 μg EE_2
			Adult: 1.25–2.5 mg CEE
30–50	Lower dose of oestrogen but providing full protection against osteroporosis		e.g. 0.625 CEE
>50	As in other postmenopausal women		

AMH, anti-Müllerian hormone; E_2, oestradiol; EE_2, ethinyl oestradiol; CEE, conjugated equine oestrogens; t/d, transdermal.

Treatment of Turner's syndrome during transition

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The optimal oestrogen formulation, dosage, route of administration, as well as the time of adding progestin treatment, still remain controversial. The overall goal of oestrogen treatment is to replicate the pace of puberty

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DOI: 10.1530/EJE-17-0430

Table 5 Recommended estrogen replacement options for feminization in adolescent TS.

Preparation	Pubertal initiation dose	Adult dosing
Transdermal E2	3–7 µg/day*	25–100 µg/day
Micronized 17β oral E2 (E2)	0.25 mg/day	1–4 mg/day
Ethinyl estradiol (EE)**	2 µg/day	10–20 µg/day
Depot E2***	0.2 mg/month	2 mg/month

Incremental dose increases can occur approximately every 6 months to mimic the normal pubertal tempo until adult dosing is reached over a 2- to 3-year period.

However, the risk of breast cancer is low in TS and long-term treatment with HRT does not seem to induce breast cancer

Once adult replacement doses are reached, treatment should persist until the risk of continuation outweighs the benefits, around the average age of menopause.

Fertilità e gravidanza, rischio complicanze

3.1. Spontaneous pregnancies

28). A study of 160 spontaneous pregnancies in 74 TS women found that, of the 58% resulting in a live birth, 34% were complicated by a fetal malformation. Of these, two-thirds were TS or Down syndrome, and the remaining etiologies were multifactorial (210). The risk rate of early pregnancy loss in the general population is 8–20% (211).

3.2. Assisted reproductive technologies (ART) with autologous oocytes

R 3.2. We suggest that young mosaic TS women with persistent ovarian function should be counseled that oocyte cryopreservation after controlled ovarian hyperstimulation is a possible fertility preservation option (⊕◯◯◯).

R 3.3. We recommend against routine oocyte retrieval for fertility preservation of young TS girls before the age of 12 years (⊕◯◯◯).

Clinical Practice Guideline | C H Gravholt and others | Turner syndrome clinical practice guideline | 177:3 | G1–G70

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting

Fertilità e gravidanza, rischio complicanze

Spontaneous pregnancies are very rare (2%) in women with TS. The likelihood of functional ovarian tissue and fertility in women with TS relies on the presence of 46,XX germ cells in the ovaries and is therefore more likely in women with mosaicism. Advances in reproductive medicine, involving *In Vitro* Fertilization—Embryo Transfer (IVF-ET), have increased the possibility of childbearing in infertile women with TS, but pregnancy remains particularly challenging due to the high prevalence of serious, life-threatening cardiovascular complications such as aortic dissection (AoD).

IVF-ET, using oocyte donation, is the most used reproductive technique and it represents the only way to become pregnant for the vast majority of such women in whom ovarian failure is likely to be established at the time of starting a family. A review of 23 women with TS following ovum donation reported a miscarriage rate of 44% and take home baby rate of 18% per transfer.[46] In a further cohort of 30 women following oocyte donation, 26% of clinical pregnancies ended in miscarriage, much lower than the miscarriage rate of 45% using the patient's own gametes.[47]

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Patologie cardiovascolari: problemi aperti

- Patologie del sistema cardiovascolare PRECOCI;
- Metodica di DIAGNOSTICA PER IMMAGINI più adeguata all'identificazione del difetto congenito/acquisito;
- Tempistica ottimale per l'esecuzione di accertamenti mirati;
- Terapia con GH ed estrogeni ed EFFETTI sul sistema CV;
- Gravidanza
  - Rischio di dissezione aortica,
  - Controindicazioni;
- Medicina di transizione.

Rischio Cardiovascolare

Rapporto Standardizzato di Mortalità per tutte le cause e per cause specifiche

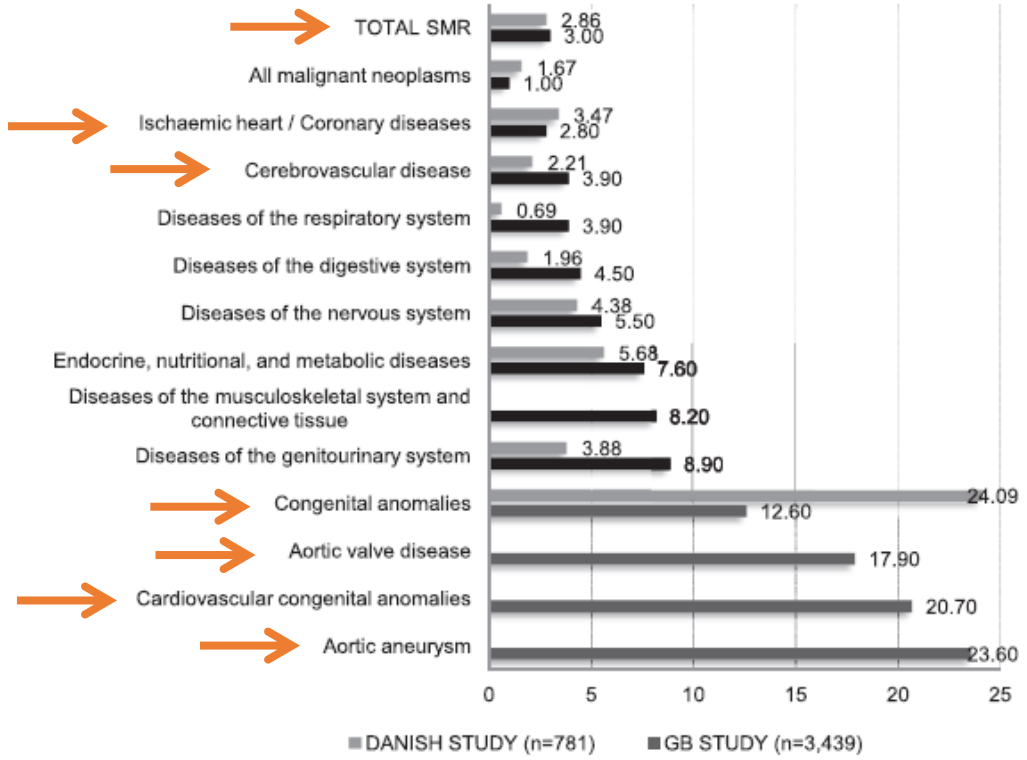


Figure 1 Total and cause-specific SMR in Turner's syndrome by main diagnostic groups, from the Denmark[2] and Great Britain[3] cohort studies data. SMR is the ratio of deaths in the study population compared with the number expected from rates in the general population. The Danish study used the ICD-10, while the study from Great Britain used ICD-9 for the classification of diagnostic groups. Some cause-specific diagnostic subcategories (e.g., diseases of musculoskeletal system, aortic valve disease, cardiovascular congenital anomalies and aortic aneurysm) were not separately included in the Danish cohort study data. The high congenital anomalies SMR in Danish cohort is likely attributable to malformations of the heart and great arterial vessels.

Marin et al. Imaging of cardiovascular risk in patients with Turner's syndrome. Clin Radiol 2015. 70:803-814.

Patologia Cardiovascolare

Panoramica di difetti cardiaci congeniti

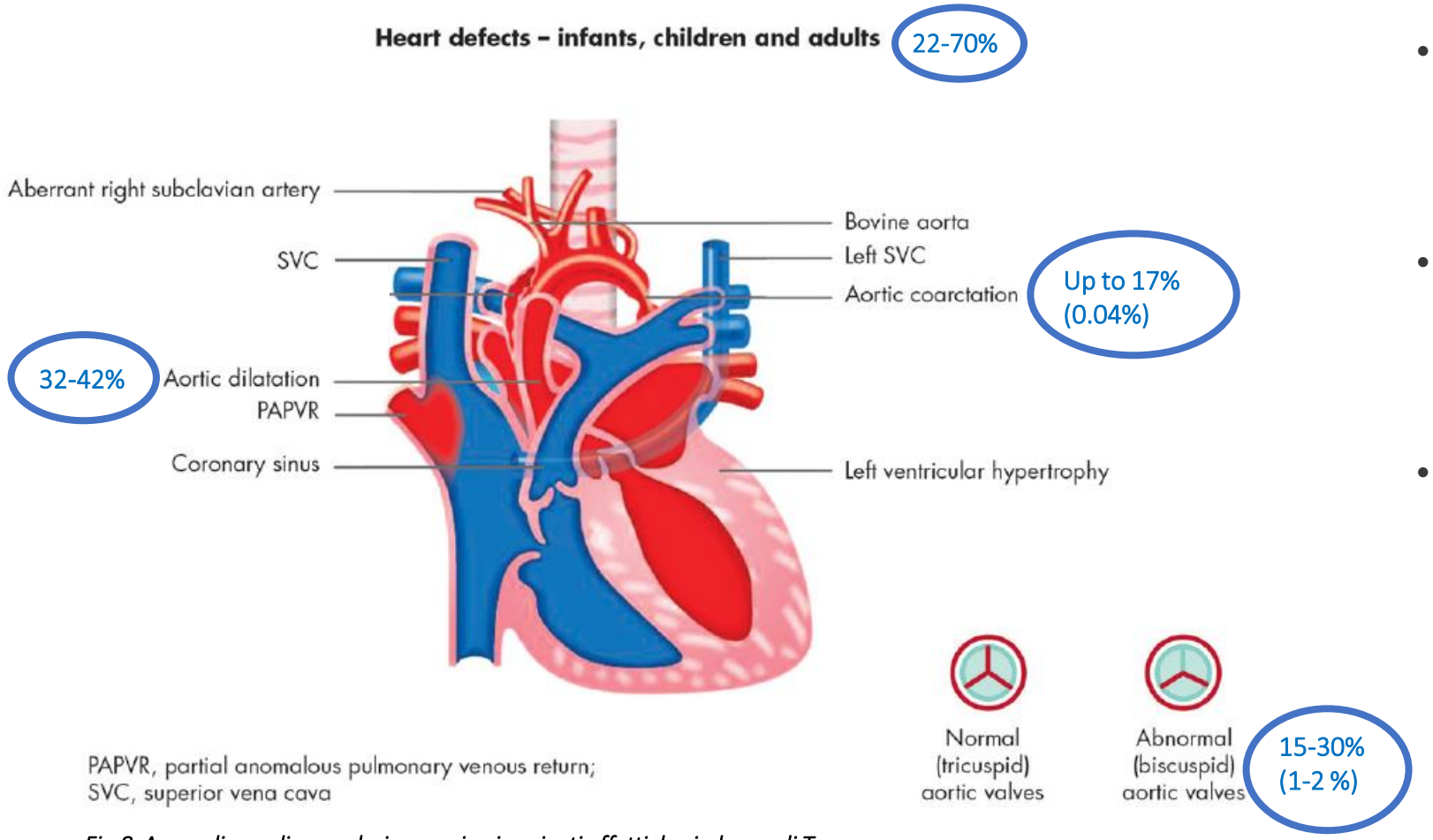


Fig.8. Anomalie cardiovascolari comuni nei pazienti affetti da sindrome di Turner.

- Principale determinante della ridotta aspettativa di vita in pazienti Turner;
- 50% dell'eccesso di morbidità attribuibile a patologia CV;
- Correlazione genotipo-fenotipo:
  - 45, X → anomalie congenite
  - Altri → patologie CV acquisite

Kristian HM, Niels HA, Claus HG. Cardiovascular Phenotype in Turner Syndrome - Integrating Cardiology, Genetics and Endocrinology. Endocrine Reviews, 2012. 33(5):677-714.

Patologia Cardiovascolare

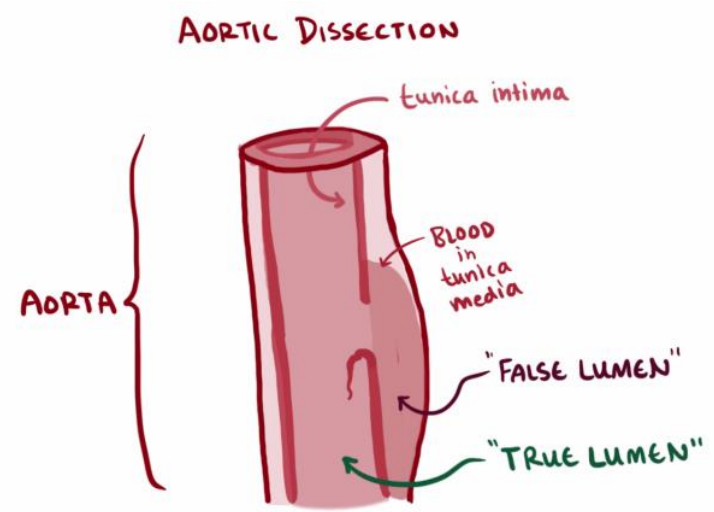
Principali difetti congeniti

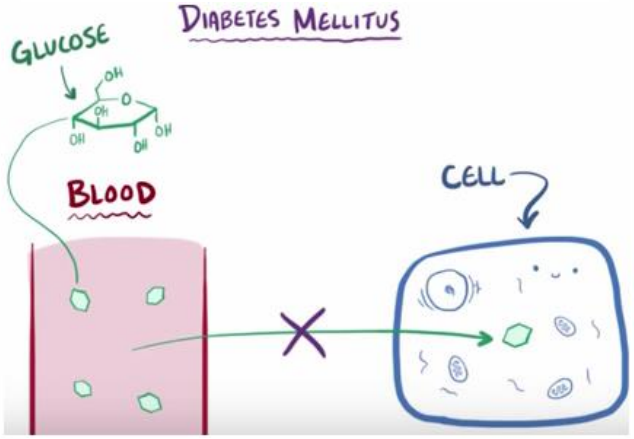
- Valvola aortica bicuspide
  - 15-30% (1-2% nella popolazione generale)
  - Il rischio di disfunzione valvolare in pazienti Turner correla con la presenza di aorta bicuspide (RR 7.9 per stenosi e RR 4.2 per insufficienza)
  - Il rischio annuale di endocardite è aumentato (0.3-2%) nella popolazione generale con aorta bicuspide (profilassi)
  - R-NC → stenosi e insufficienza; R-L → coartazione Ao, dilatazione
- Coartazione aortica
  - 17% (0.04% nella popolazione generale)
  - Spesso coesiste aorta bicuspide (RR 4.6); spesso fa parte di un fenotipo aortico anomale (kinking, elongated aortic arch, aorta bovina, arco aortico cervicale …)
  - Problematiche relative alla tecnica di correzione nei pazienti Turner e rischio residuo di dissezione aortica.

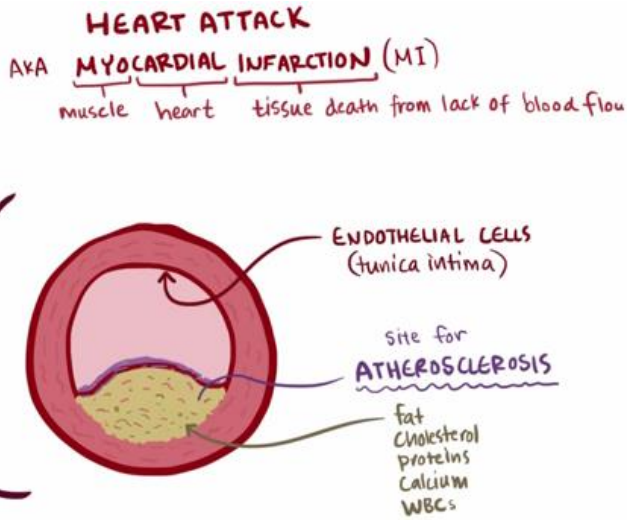
Kristian HM, Niels HA, Claus HG. Cardiovascular Phenotype in Turner Syndrome - Integrating Cardiology, Genetics and Endocrinology. Endocrine Reviews, 2012. 33(5):677-714.

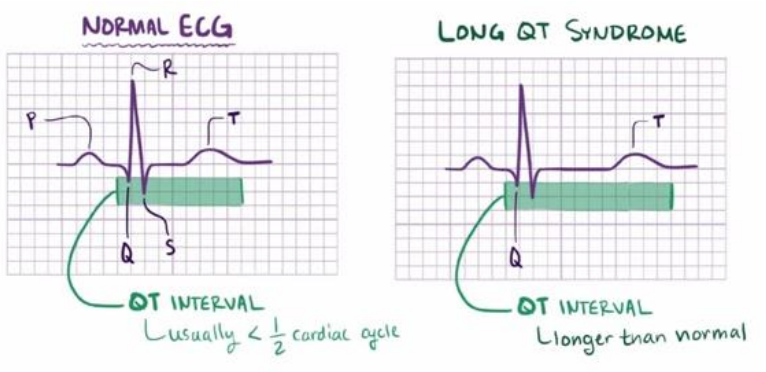
Patologia Cardiovascolare

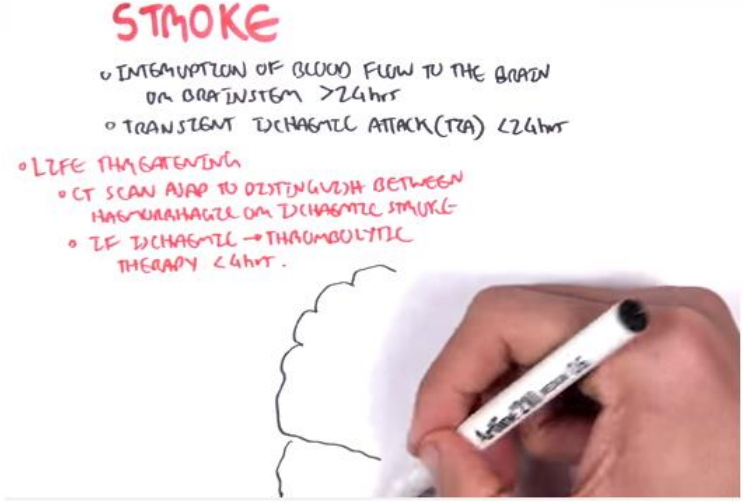
Panoramica di difetti cardiaci acquisiti

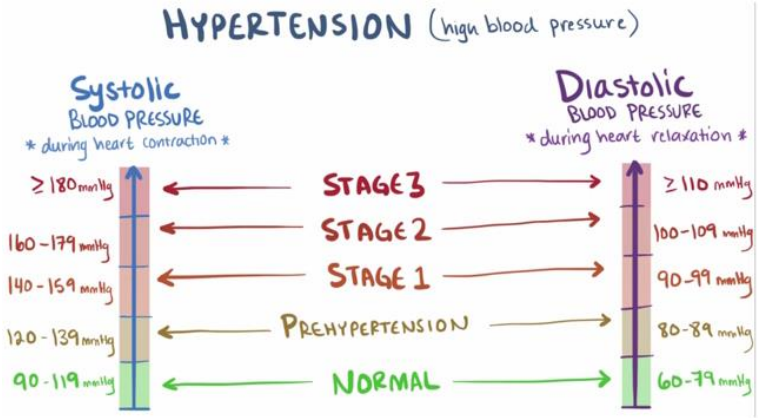












Patologia Cardiovascolare

Principali difetti cardiaci acquisiti

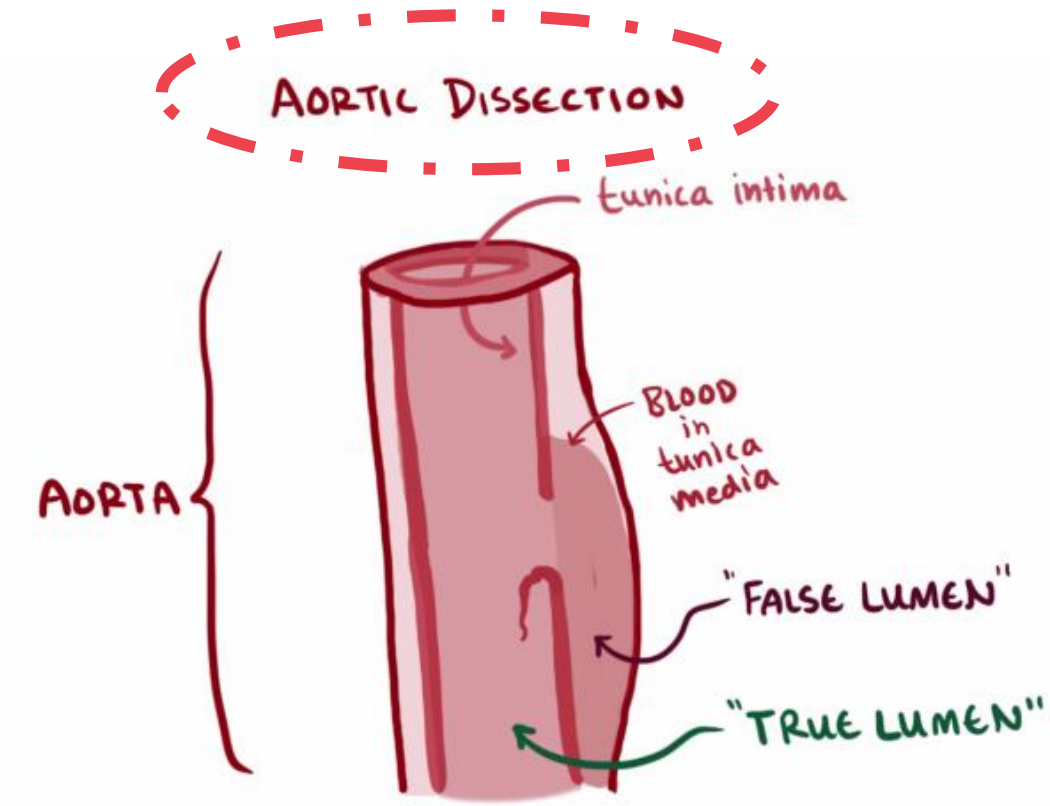


Fig.10. *Rappresentazione schematica di dissezione aortica. Open.osmosis.org*

- Rischio x100 rispetto alla popolazione generale
- Età media 30.5 anni vs. 77 nella pop. generale
- Fattori di rischio: ipertensione, dilatazione, coartazione, aorta bicuspide.
- **DILATAZIONE AORTICA**:
  - AD/DD ratio (> 1.5)
  - ASI = diametro aortico/superficie corporea (>2 cm/mq = aneurisma)

Marin et al. Imaging of cardiovascular risk in patients with Turner's syndrome. Clin Radiol 2015. 70:803-814.

Patologia Cardiovascolare

Principali difetti cardiaci acquisiti – Dissezione aortica

•Velocità di crescita del diametro dell'aorta ascendente: 0.24- 1.22 mm/anno (Eco) 0.1-0.4 mm/anno (RMN) vs. 0.07 mm/anno nelle donne con cariotipo normale, 0.1 mm/anno negli aneurismi dell'aorta toracica, 0.2 mm/anno nella bicuspidia valvolare aortica.

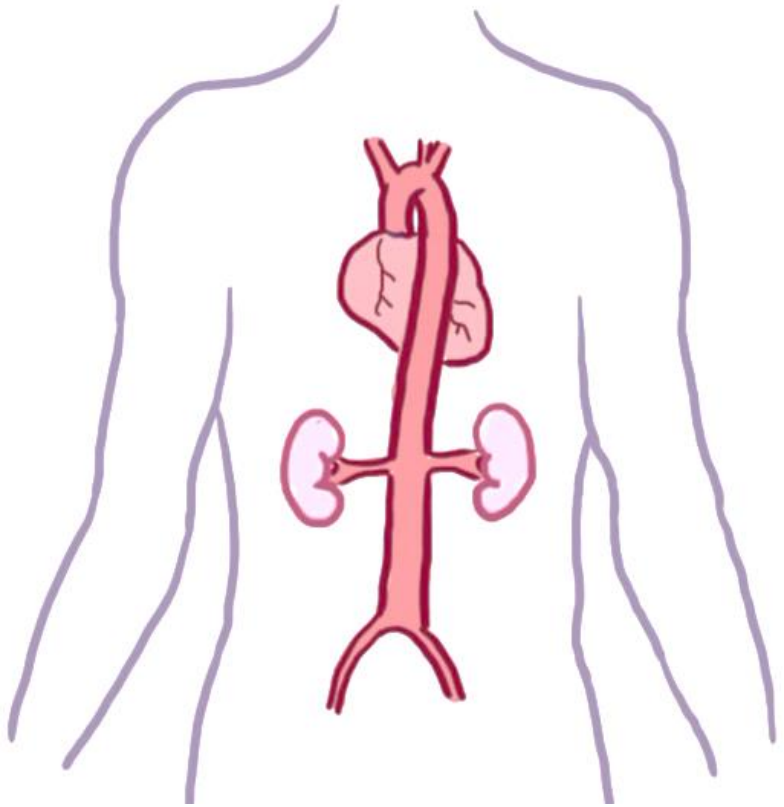


Fig.11. *Aorta toracica e addominale. Open.osmosis.org*

Marin et al. Imaging of cardiovascular risk in patients with Turner's syndrome. Clin Radiol 2015. 70:803-814.

Patologia Cardiovascolare

Principali difetti cardiaci acquisiti – Dissezione aortica

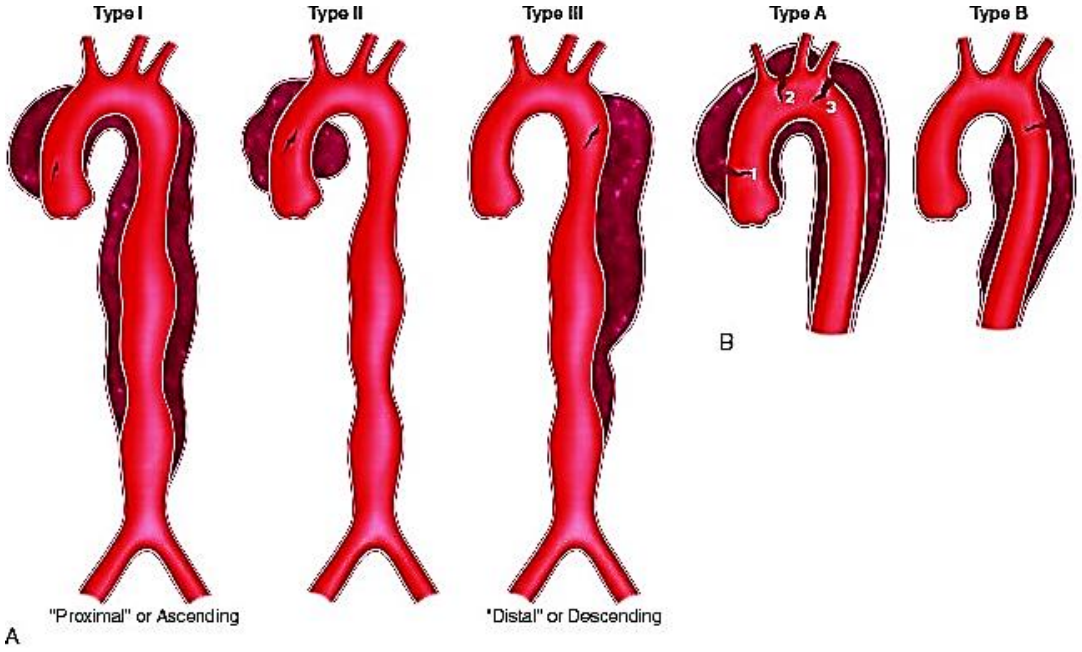


Fig.11. Classificazione di Stanford (B) e di DeBakey (A) della dissezione aortica.
A) I. Origina dall'aorta ascendente e si propaga alla discendente; II. confinata all'aorta ascendente; IIIa. Confinata all'aorta toracica discendente; IIIb. coinvolge l'aorta toracica discendente e si estende all'aorta addominale.
B) tipo A, coinvolge l'aorta ascendente; tipo B, limitata all'aorta discendente.

- Nel 63% dei casi, gli episodi di dissezione aortica interessano **l'aorta** ascendente (Stanford A e DeBakey I e II),
- Emergenza chirurgica con prognosi sfavorevole
  - Sostituzione aorta ascendente
  - Come sopra + sostituziane valvolare (Bentall)
  - Sostituzione AA + reimpianto TSA
- Diagnosi: TC con mdc toraco-addominale

Marin et al. Imaging of cardiovascular risk in patients with Turner's syndrome. Clin Radiol 2015. 70:803-814.
Novaro GM. Diseases of the Aorta. Cleveland Clinic – Desease Management. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/diseases-of-the-aorta/
Kapustin AJ, Litt HI. Diagnostic imaging for aortic dissection. Semin Thorac Cardiovasc Surg 2005; 17:214–223.

Patologia Cardiovascolare

Principali difetti acquisiti

- **Ipertensione arteriosa sistemica**
  - Essenziale, multifattoriale (iperattività simpatica, difetto estrogeni, resistenza insulinica, adiposità viscerale, difetto di o resistenza al GH, SRAA?)
  - 21-40% delle bambine e adolescenti, 50-58% delle donne adulte Turner
  - Solo il 4-22% riceve adeguato trattamento (Beta blocco? Alfa e beta blocco? Antagonisti del recettore per l'angiotensina?)
- **Cardiopatia ischemica**
  - Multifattoriale (ipertensione, dislipidemia, resistenza insulinica e diabete, obesità, deficit di estrogeni e/o di GH, stati di ipercoaguilabilità)

Kristian HM, Niels HA, Claus HG. Cardiovascular Phenotype in Turner Syndrome - Integrating Cardiology, Genetics and Endocrinology. Endocrine Reviews, 2012. 33(5):677-714.
Landin-Wilhelmsen K, Bryman I, Wilhelmsen L 2001 Cardiac malformations and hypertension, but not metabolic risk factors, are common in Turner syndrome. J Clin Endocrinol Metab 86:4166–4170

Patologia Cardiovascolare

Principali difetti acquisiti

- **Aritmie**
  - QT > 440 msec nel 33-36% delle bambine e nel 21% delle donne adulte Turner.
- **Stroke**
  - 2^ decade di vita (precoce!); 90% delle morti dovute a s. emorragico
  - Early CV aging + disequilibrio metabolico + scorretto dosaggio terapie sostitutive GH ed estrogeni + aterosclerosi precoce + eventi cardio-embolici + coagulopatie …
- **Dismetabolismo**
  - Ridotta tolleranza al glucosio, DM2 (43% delle Turner con isocromosoma Xq), obesità, difetto di estrogeni e difetto/resistenza GH.

Kristian HM, Niels HA, Claus HG. Cardiovascular Phenotype in Turner Syndrome - Integrating Cardiology, Genetics and Endocrinology. Endocrine Reviews, 2012. 33(5):677-714.

Patologia Cardiovascolare

Ipotesi Eziopatogenetiche

- Aplo-insufficienza del gene SHOX → BNP, FGFR3
- Correlazione causale tra ipoplasia linfatica, linfedema e cardiopatia congenita
- Difetto primitivo della cresta neurale, responsabile di entrambe le anomalie cardiache e linfatiche
- Difetto di TGF-beta2
- Ruolo di TGF-beta1 e di SMAD2
- Altro: biglicani, VEGF …

Marchini A et Al. BNP is a transcriptional target of the short stature homeobox gene SHOX. Hum Mol Genet 16:3081–3087
Gravholt CH et Al. Nocturnal hypertension and impaired sympathovagal tone in Turner syndrome. J Hypertens 24:353–360
Clark EB 1984 Neck web and congenital heart defects: a pathogenic association in 45 X-O Turner syndrome? Teratology 29:355–361
Goumans MJ, Liu Z, ten Dijke P 2009 TGF- signaling in vascular biology and dysfunction. Cell Res 19:116–127
Bondy CA 2008 Congenital cardiovascular disease in Turner syndrome. Congenit Heart Dis 3:2–15
Gomez D, et Al. Syndromic and non-syndromic aneurysms of the human ascending aorta share activation of the Smad2 pathway. J Pathol 218:131–142.
Miyabara S, Nakayama M, Suzumori K, et al. Developmental analysis of cardiovascular system of 45,X fetuses with cystic hygroma. Am J Med Genet 1997;68:135e41

Rischio Cardiovascolare

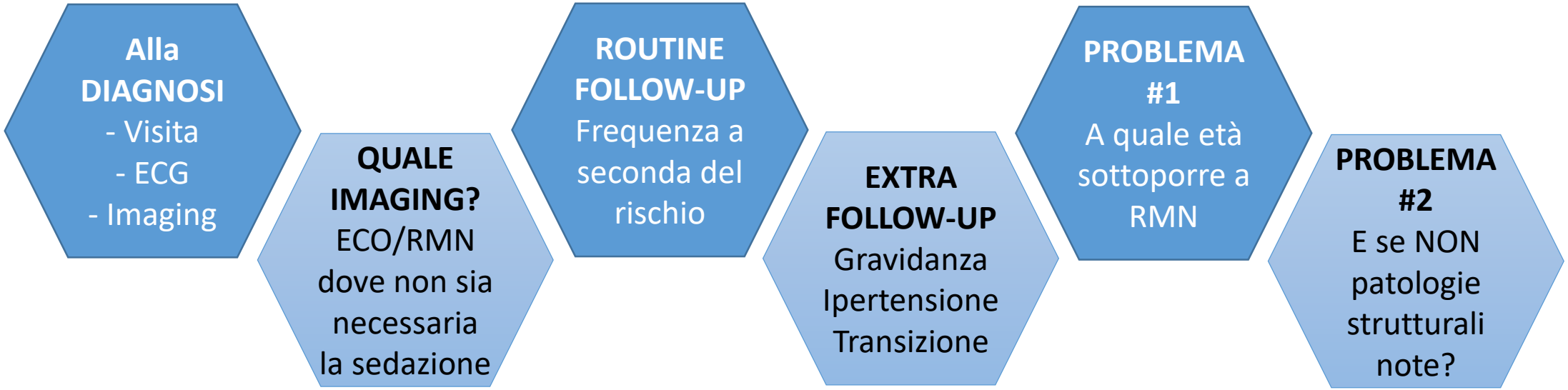
Prevenzione Secondaria

- Importanza di sottoporre a screening CV la fascia di età più giovane → la dilatazione aortica può manifestarsi già in bambine di 5 anni;
- Anche se NON evidenza di anomalie strutturali in utero, è indicato imaging post-natale (la bicuspidia e la CoAo spesso non si apprezzano all'eco fetale);
- Follow-up cardiologico di anomalie strutturali e non (semestrale o annuale) + RMN ogni 3-5 aa;
- In assenza di patologia CV in anamnesi, follow-up clinico annuale con misurazione della Pa e visita cardiologica con ECG, ECOCG e/o RMN ogni 5 anni alla transizione alla medicina dell'adulto e prima di ogni gravidanza);
- Long-term care, multispecialistica.

Marin et al. Imaging of cardiovascular risk in patients with Turner's syndrome. Clin Radiol 2015. 70:803-814.
Sharma J et al. Aortic distensibility and dilation in Turner's Syndrome. Cardiol Young 2009; 19(6):568-72.

Rischio Cardiovascolare

Flow-chart – screening e follow-up della patologia cardiovascolare



Rischio Cardiovascolare

Prevenzione secondaria - Imaging

Ecocardiogramma

- Tecnica di scelta in neonati, lattanti e durante la 1^ e 2^ infanzia per la sua disponibilità, il basso costo, la precisione e l'affidabilità;
- Individua condizioni ad alto rischio per la vita e le complicanze che ne derivano;
- Difficoltà nel visualizzare: vena polmonare superiore sx, aorta toracica distale alla porzione ascendente;
- Finestra ecografica subottimale per la caratteristica corporatura della paziente con TS.

Risonanza Magnetica

- Viene in aiuto in caso di visualizzazione parziale o scadente dell'anatomia CV mediante ECOCG;
- Rivela anomalie clinicamente silenti o non apprezzabili mediante tecnica ecografica;
- Ogni bambina > 12 aa (capacità di tollerare l'esame senza necessità di sedazione).

Marin et al. Imaging of cardiovascular risk in patients with Turner's syndrome. Clin Radiol 2015. 70:803-814.

GH therapy and CV risk

Estrogen therapy and CV risk

Timing

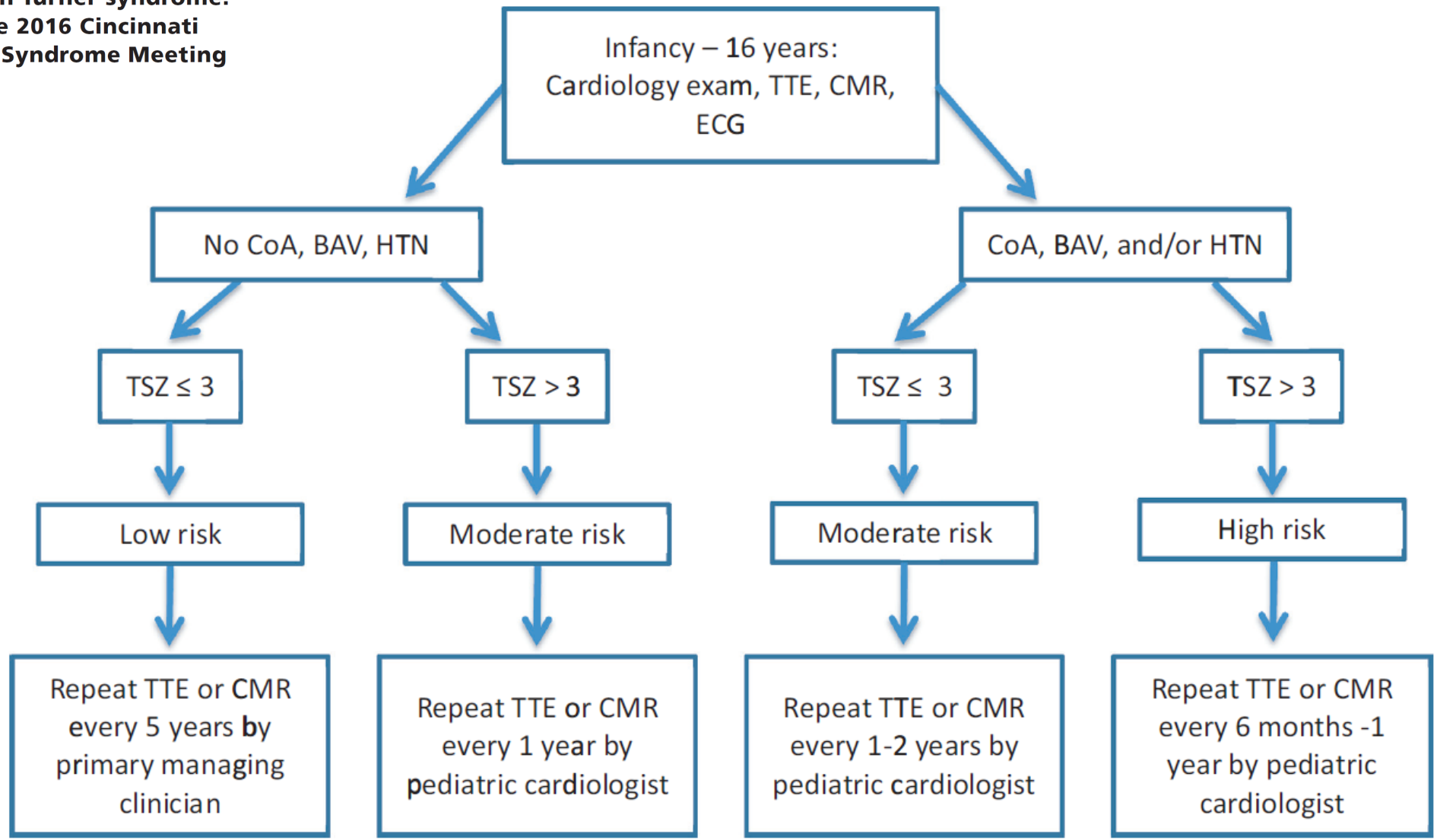
Role of "candidate genes"

Pregnancy

Lack of pediatric evidence and limited insight on cardiovascular phenotype in TS

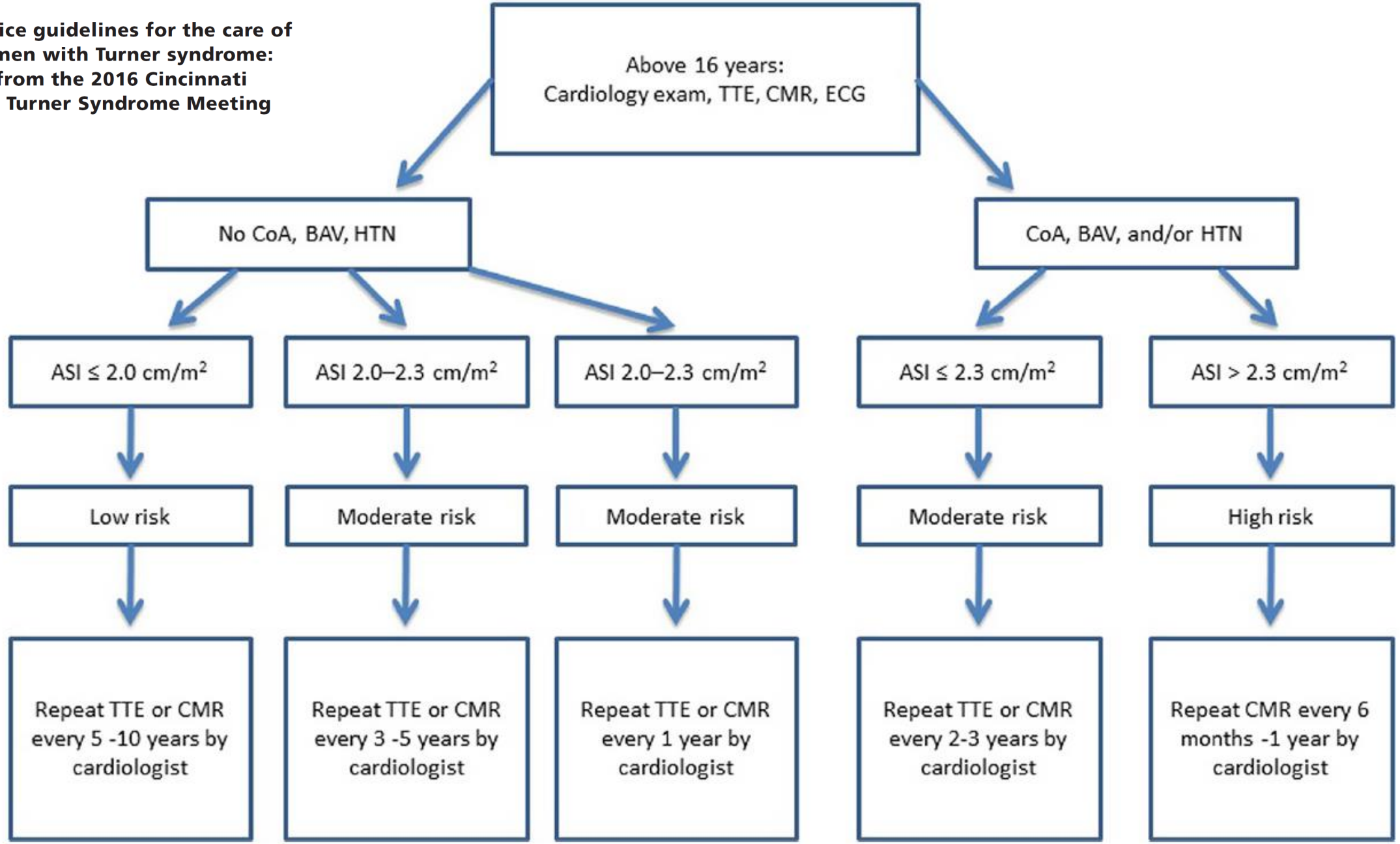
Transition Medicine

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting



TTE: transthoracic echocardiography. CMR: cardiac magnetic resonance imaging. ECG: electrocardiogram. CoA: coarctation of aorta. BAV: bicuspid aortic valve. HTN: hypertension. TSZ: Turner syndrome specific Z-score of the aorta (see text for explanation).

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting



GH therapy and CV risk

Estrogen therapy and CV risk

Role of "candidate genes"

Timing

Pregnancy

Lack of pediatric evidence and limited insight on cardiovascular phenotype in TS

Transition Medicine

Rischio Cardiovascolare

Effetti della terapia estrogenica sul sistema cardiovascolare

Benefici

- Contribuisce alla crescita staturale
- Sviluppo dei caratteri sessuali
- ↓ rischio CV (profilo lipidico e rigidità aortica)
- Migliora la densità minerale ossea
- Migliora le funzioni mnemoniche e cognitive
- Favorisce la riduzione degli enzimi epatici
- Incrementa la forza muscolare
- Non ha effetti sulla pressione
- Essenziale alla normale omeostasi glucidica
- Immunomodulazione

Negativi

- Coagulopatia e rischio di eventi trombo-embolici
- Rischio di sviluppare carcinoma mammario?

Kristian HM, Niels HA, Claus HG. Cardiovascular Phenotype in Turner Syndrome - Integrating Cardiology, Genetics and Endocrinology. Endocrine Reviews, 2012. 33(5):677-714.
Backeljauw P. Management of Turner Syndrome. UpToDate, 2016.

Rischio Cardiovascolare

Effetti della terapia con GH sul sistema cardiovascolare

Benefici

- Guadagno staturale
- Migliora la composizione corporea (riduzione t. adiposo viscerale)
- Possibile miglioramento della funzione epatica
- Migliora la densità minerale ossea
- Non si associa con una maggiore dilatazione aortica
- Non ha effetto sulla pressione arteriosa

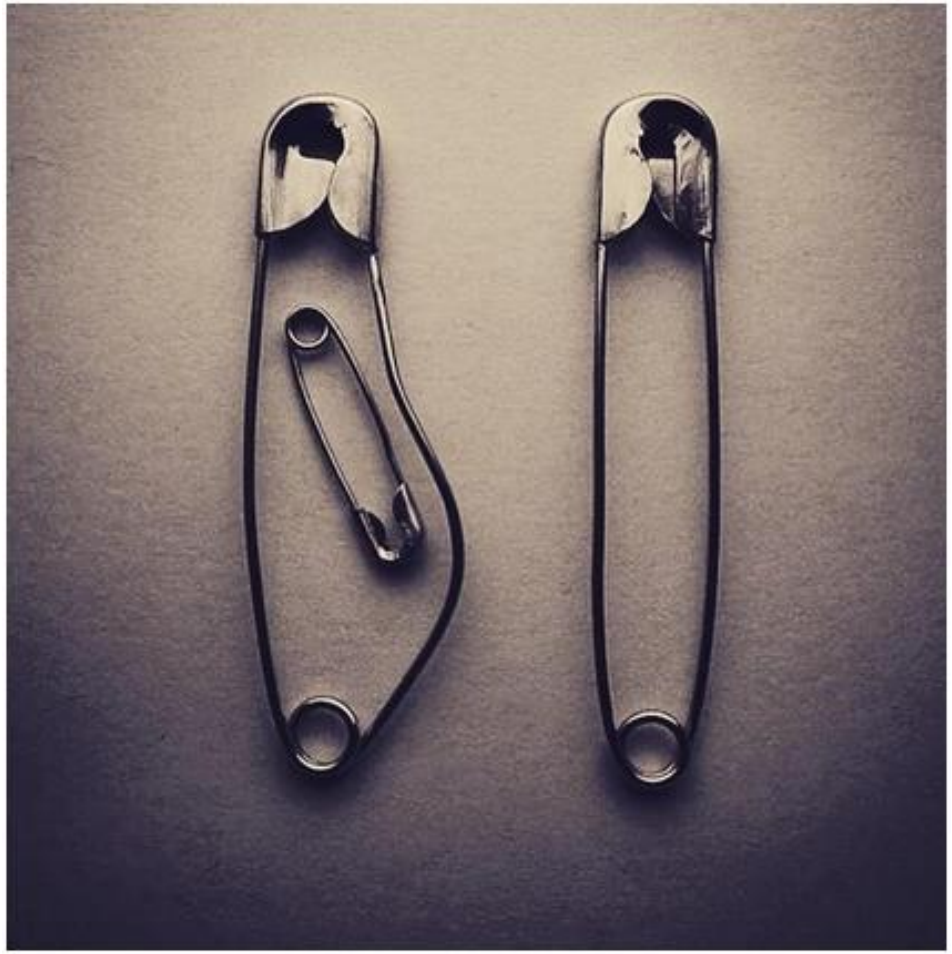
Negativi

- Riduzione sensibilità insulinica
- Ipersecrezione → potenziali effetti negativi sulle morbilità e mortalità cardiovascolare (acromegalia)
- Scoliosi già presente resa più manifesta

Kristian HM, Niels HA, Claus HG. Cardiovascular Phenotype in Turner Syndrome - Integrating Cardiology, Genetics and Endocrinology. Endocrine Reviews, 2012. 33(5):677-714.
Backeljauw P. Management of Turner Syndrome. UpToDate, 2016.

Rischio Cardiovascolare

Gravidanza



- Il rischio di dissezione aortica può raggiungere il 10% ed è aumentato nel terzo trimestre;
- Il 50% delle dissezioni avvengono durante il terzo trimestre (consigliata ECO mensile) oppure durante il puerperio;
- Se incremento del diametro Ao ≥ 10% → RMN
- Mortalità 86%;
- Check up completo in ogni donna Turner che desideri una gravidanza.

Cabanes L et al. Turner Syndrome and pregnancy: clinical practice. Recommendations for the management of patients with TS before and during pregnancy. European J of Obstetrics & Gynecology 2010;152:18-24.

Fertilità e gravidanza

Table 4 International expert consensus in recommendations of CVS risk contraindicating pregnancy in TS

Consensus	Recommendations	Criteria
American Society for Reproductive Medicine (2012)	Absolute contraindication	Any significant cardiac abnormality and/or ASI >2 cm/m^2
French College of Obstetricians and Gynaecologists (2010)	Contraindication	History of aortic surgery Previous aortic dissection Aortic dilatation (ASI >2.5 cm/m^2 or absolute dimensions >3.5 cm) Coarctation of aorta Uncontrolled hypertension despite medical treatment

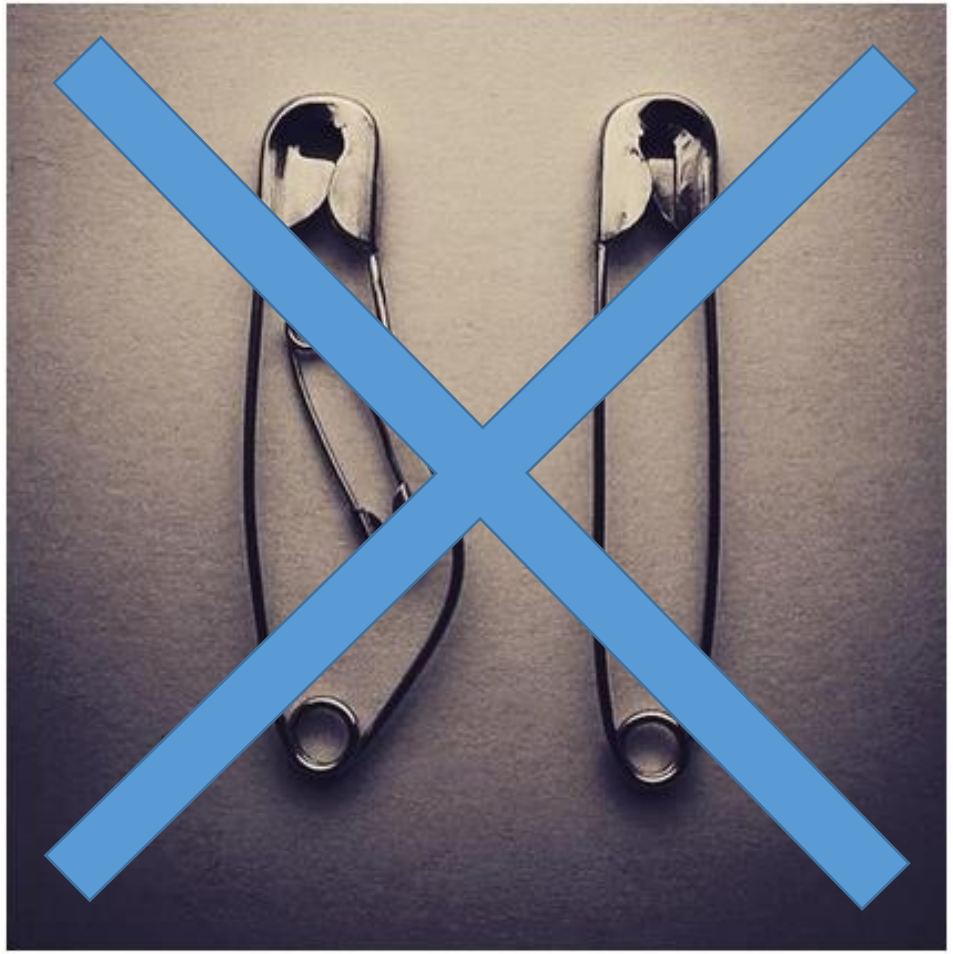
British Medical Bulletin, 2015, **113**:45–58
doi: 10.1093/bmb/ldu038
Advance Access Publication Date: 22 December 2014

Turner syndrome–issues to consider for transition to adulthood

Laura Lucaccioni[†], Sze Choong Wong[†], Arlene Smyth[‡], Helen Lyall[§], Anna Dominiczak[**], S. Faisal Ahmed[†], and Avril Mason[†,*]

Rischio Cardiovascolare

Gravidanza



CONTROINDICAZIONI ALLA GRAVIDANZA

1. Storia di chirurgia aortica
2. Storia di dissezione aortica
3. Dilatazione aortica con il massimo diametro misurabile > 25 mm/mq o > 35 mm
4. Coartazione aortica
5. Ipertensione non controllata da terapia medica ottimale
6. Chirurgia della valvola aortica

Cabanes L et al. Turner Syndrome and pregnancy: clinical practice. Recommendations for the management of patients with TS before and during pregnancy. European J of Obstetrics & Gynecology 2010;152:18-24.

- Scarsa compliance e perdita al follow-up
- Tarda adolescenza
- Percorso graduale
- Comportamenti volti alla cura di sé
- Adult care plan

Bondy CA. Care of girls and women with TS: a guideline of the TS study group. The Journal of Clinical Endocrinology & Metabolism 2007; 92(1):10-25.

Review | A Gawlik and E Malecka-Tendera | Turner's syndrome during transition | 170:2 | R57–R74

TRANSITION IN ENDOCRINOLOGY

Treatment of Turner's syndrome during transition

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Concluding remarks

The transition period should be initiated as a staged process. At the age of 12–13 years, care should be shifted from the parent to the TS teenager. The adolescent patients should be informed about all aspects of adult TS life, risk of complications and the need for regular follow-up and preventive health care. TS is a condition associated with high risk of short stature, cardiovascular diseases, ovarian failure, osteoporosis, hearing loss, diabetes mellitus and hypothyroidism and as such requires the attention of a multidisciplinary team (Table 1). Accordingly, upon transfer to an adult care clinic, the young woman with TS should undergo a comprehensive medical evaluation including screening for hypertension, diabetes, dyslipidemia and osteoporosis. Most importantly, all medical problems present during childhood should be followed in adult life, with special attention being paid to congenital cardiovascular disorders, such as thyroid and celiac diseases and hearing loss.

Table 6 Recommendations for screening in Turner syndrome at diagnosis and throughout life (excluding those covered elsewhere, i.e. cardiac and neuropsychological).

	At diagnosis	**After diagnosis** (childhood)	**After diagnosis** (adults)
Weight/BMI	Yes	Every visit	Every visit
Blood pressure	Yes	Every visit	Every visit
Thyroid function (TSH and (free) T4)	Yes	Annually	Annually
Lipids			Annually if at least one cardiovascular risk factor[¤] or regional recommendation
Aminotransferase, GGT and alkaline phosphatase		Annually after 10 years of age	Annually
HbA1c with or without fasting plasma glucose		Annually after 10 years of age	Annually
25-Hydroxyvitamin D		Every 2–3 years after 9–11 years of age	Every 3–5 years
Celiac screen		Starting at 2 years; thereafter every two years	With suggestive symptoms
Renal ultrasound	Yes		
Audiometric evaluation	Yes*	Every 3 years	Every 5 years
Ophthalmological examination	Yes[#]		
Dental evaluation	Yes, if no previous care has been established		
Clinical investigation for congenital hip dysplasia	Yes, in newborns		
Skin examination	At diagnosis	Annually	Annually
Bone mineral density			Every 5 years and when discontinuing estrogen
Skeletal assessment		5–6 years and 12–14 years (see 6.1.10.)	

	Action	Suggested frequency	Comments
Obesity	Weight	Annually	Many comorbidities are weight-related, e.g., diabetes, elevated cholesterol, and liver dysfunction. Weight management is the most important health intervention at annual visits. Obesity may be due to low physical fitness, sedentary lifestyle, and poor food choices
Cardiovascular	Echocardiogram	3–5 years – yearly if aortic root >3 cm	Management shared with GUCH (Grown-ups with congenital heart defects) clinic preferable. Congenital malformations include bicuspid aortic valve, coarctation of the aorta, and aortic dilatation
	MRI aorta	As appropriate	Some units use echocardiography for routine monitoring and reserve MRI for ambiguous findings or as part of pre-pregnancy assessment. The place of MRI scanning depends on expertise of the echocardiography service
	Blood pressure	Annually	Hypertension affects up to 50% of young adults and contributes to the risk of aortic dissection. Refer to age-specific reference data. Hypertension can be treated to normal guidelines including use of beta-blockers or angiotensin receptor blockers. For aortic root >3.0 cm and BAV, aim for systolic blood pressure <140 mmHg if tricuspid aortic valve or <120 mmHg if bicuspid valve
Bone metabolism	DEXA scan	Every 5 years	Estrogen replacement required until ~50 years (or older if there have been many years of estrogen deficiency) to prevent osteoporosis. Bone density of spine reads low in short stature with DEXA. Osteoporosis can be treated as in other situations
	Vitamin D and calcium profile	3–5 years	Monitor bone profile in those with low calcium and low vitamin D levels; exclude celiac disease (see below)
Liver	Liver function tests	Annually	Liver enzymes, especially gammaglutamyl transaminase (GGT), are commonly elevated. Slowly progressive, but improves with estrogen and weight loss. Consider viral screen for acute changes (rarely positive)
	Liver ultrasound	As appropriate	Liver US required for markedly raised (GGT), alkaline phosphatase or transaminases. Consider special scans measuring fibrosis and steatosis, and biopsy if structural defects identified on US

Clinical Practice Guideline | C H Gravholt and others | Turner syndrome clinical practice guideline | 177:3 | G1–G70

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting

Diabetes	HbA1c ± fasting plasma glucose	Annually	Consider OGTT if HbA1c is elevated. High risk of developing impaired glucose tolerance (50%) due a combination of insulin deficiency and insulin resistance. Fasting plasmaglucose underestimates defect of insulin secretion
Fertility	Adoption and oocyte donation education	As appropriate	Spontaneous pregnancy occurs in 2–5%. Ovarian failure occurs in 90%. Medical review on advisability of pregnancy with regard to risk of aortic dissection is required
	Uterine ultrasound	As appropriate	US of the uterus should take place on arrival in the adult clinic and again during the work-up for pregnancy
Psychological	Review psychological issues	As appropriate	Increased risk of social isolation, anxiety, and obsessive behavior. Higher levels of shyness and social anxiety, and reduced self-esteem. Review problems in work place or in relationships. Problems are responsive to clinical psychology support. See Section 7 and Tables 9 and 10
Audiology	Audiogram ENT History	3–5 years	Deafness is common and under reported. Self-reporting unreliable. Otitis media is common in childhood (60–80%) which can lead to conductive hearing loss. Sensorineural hearing loss common and progressive in adults
Dermatology	Skin inspection	Annually	Assess for keloid and changes and in pigmented nevi
Orthodontics	Teeth inspection	Annually	Referral recommended if required
Blood tests	Thyroid function	Annually	Increased risk of autoimmune thyroiditis. In hypothyroidism (24%) or hyperthyroidism (2.5%) include TPO antibodies if previously negative
	Celiac screen	With suggestive symptoms	Increased risk (4–6%) of celiac disease. Check transglutaminase IgA antibodies (and total IgA) and vitamin B12

Clinical Practice Guideline | C H Gravholt and others | Turner syndrome clinical practice guideline | 177:3 | G1–G70

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting


Grazie