Le amenorree nelle varie età della vita

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Amenorree : cause

anatomiche

Malformative :
adolescenza
e giovani donne

Altra patologia uterina :
Sinechie
Chirurgia
Esiti di radioterapia
Post partum
Infezioni

Età fertile o avanzata
(rara in adolescenza)

ipotalamiche

Primarie
Ipogonadotrope
(da ipogonadismo-ipogonadotropo)
Adolescenza
Giovani donne
D.D.
tra ritardo puberale e deficit puberale

Secondarie
Ipo-gonadotrope

da ipogonadismo-ipogonadotropo
da cause funzionali
dall'adolescenza all'età fertile

ovariche

Patologie interferenti su funzione ovarica

Primarie
ipergonadotrope

POI -POF

Diagnosi precoce:
In utero (genetica)
Infanzia
adolescenza

Post menarcali
fino a
periodo fertile avanzato

amenorree

I marcatori endocrini

Cause Anatomiche

Normale funzione ovarica

Ipotalamiche

FSH ⬇➡

Ipotalamo-ipofisarie

PRL ⬆

Da cause ovariche

FSH⬆ > 25 U/L

⬇AMH ng /ml

⬇ inhibin A and inhibin B

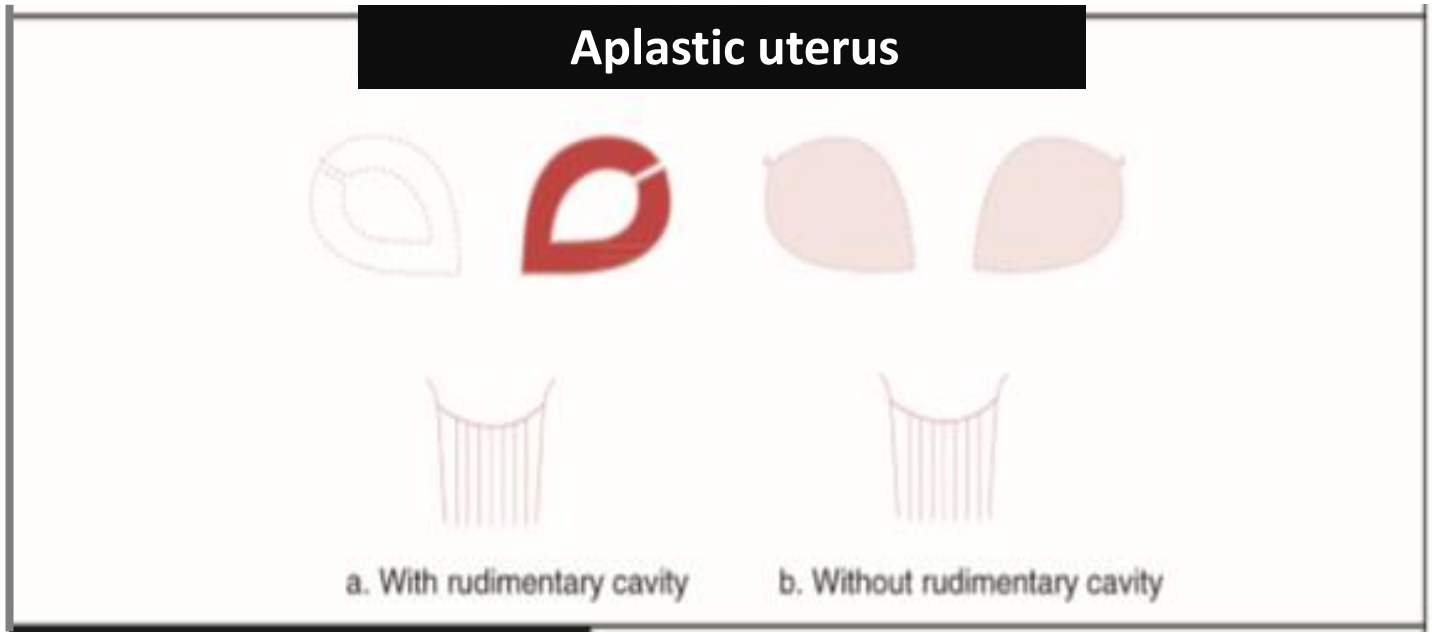
⬇ Ovarian follicle reserve (ultrasound)

Amenorrea da cause anatomiche

Espressione clinica : amenorrea primaria

Patologia malformativa — Severa ipoplasia uterina (utero aplastico) + ipoplasia vaginale

The ESHRE/ESGE classification of female genital malformations



Espressione clinica : amenorrea secondaria

Altra patologia — Sinechie intrauterine , talora con accollamento delle pareti, obliterazione della cavità e della normale struttura endometriale

Curettage per aborto indotto o spontaneo o post-partum (complicazioni) , Infezioni (tubercolosi genitale) ,chirurgia uterina , altri traumi (miomectomia)

…… indicazioni diagnostiche

Completo sviluppo dei caratteri sessuali secondari
Età ≥ 15 anni

mancato menarca

Assenza di dolore pelvico importante

Talora vaga sintomatologia algica pelvica periodica

Paziente asintomatica

Escludere patologia malformativa Tratto genitale inferiore

In particolare escludere aplasia uterina In presenza di ovaie funzionanti

Escludere altri difetti a livello uterino

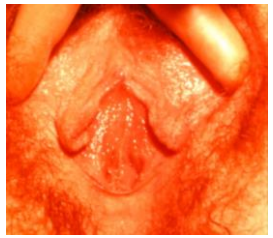
Esiti di chirurgia o radioterapia
Endometriti ,TBC a localizzazione endometriale

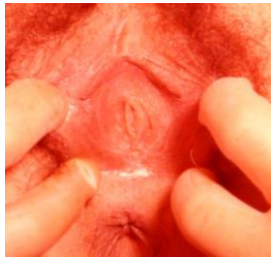
Valutazione Clinica
Genitali esterni

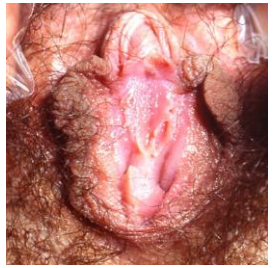
Valutazione ecografica
Genitali interni

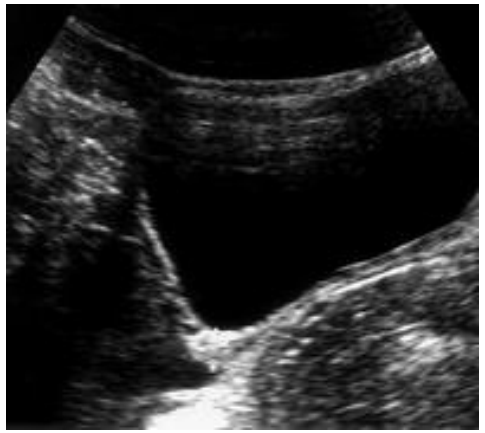
Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome.

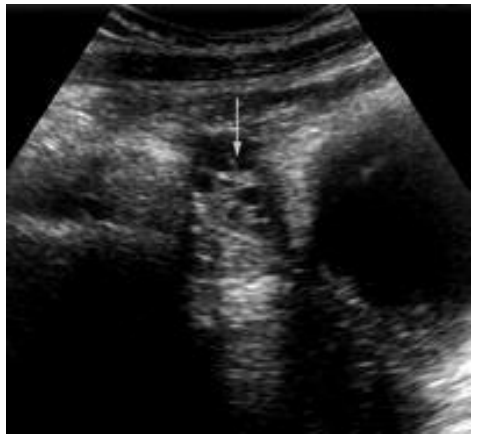
Aplasia uterina
+
Aplasia (o agenesia) vagina









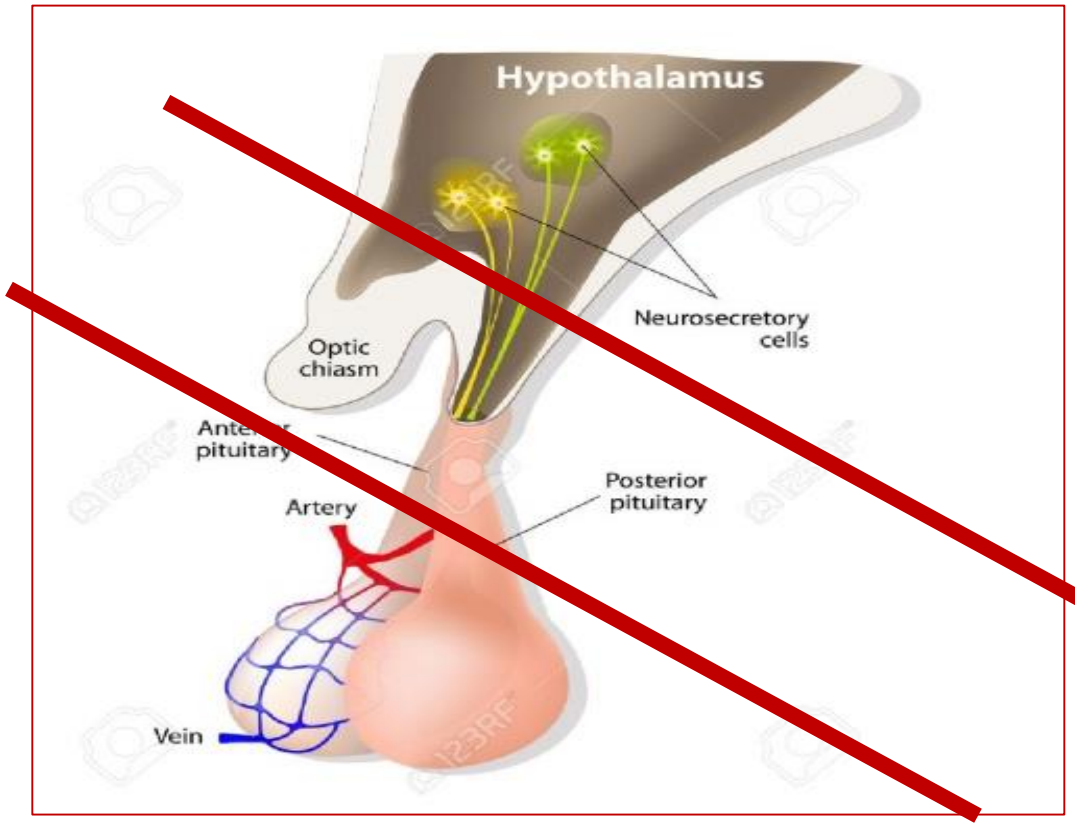


Forma tipica : no malformazioni associate

Forma atipica : con malformazioni app. urinario e ovaio

MURCS
(Mullerian duct aplasia,
Renal aplasia,
Cervicothoracic Somite displasia)

Amenorrea da cause centrali



- Congenital malformation
- Genetic conditions
- Pituitary gland or stalk damage
- Forme funzionali
- Patologia tiroidea
- Patologia surrenalica

CLINICAL PRACTICE GUIDELINE

Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline

Catherine M. Gordon,[1] Kathryn E. Ackerman,[2,5] Sarah L. Berga,[3] Jay R. Kaplan,[3] George Mastorakos,[4] Madhusmita Misra,[5] M. Hassan Murad,[6] Nanette F. Santoro,[7] and Michelle P. Warren[8]

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2017

Amenorrea primaria da ipogonadismo ipo-gonadotropo

Gordon CM et Al 2017

FSH ⬇ ⬇

Normale riserva ovarica

AMH rilevabile

Congenital malformation

Septo-optic dysplasia
Holoprosencephaly
Encephalocele

Genetic conditions

- Congenital deficiency of hypothalamic or pituitary transcription factors (gonadotropin deficiency)
- Single-gene mutations

(hypogonadotropic hypogonadism)

Diagnostica differenziale con **Ritardo Costituzionale di Crescita e Pubertà**

In qualche caso difficile (soprattutto in assenza di ipopituitarismo o anosmia)

Amenorrea primaria da ipogonadismo ipo-gonadotropo vs Ritardo Costituzionale di Crescita e Pubertà

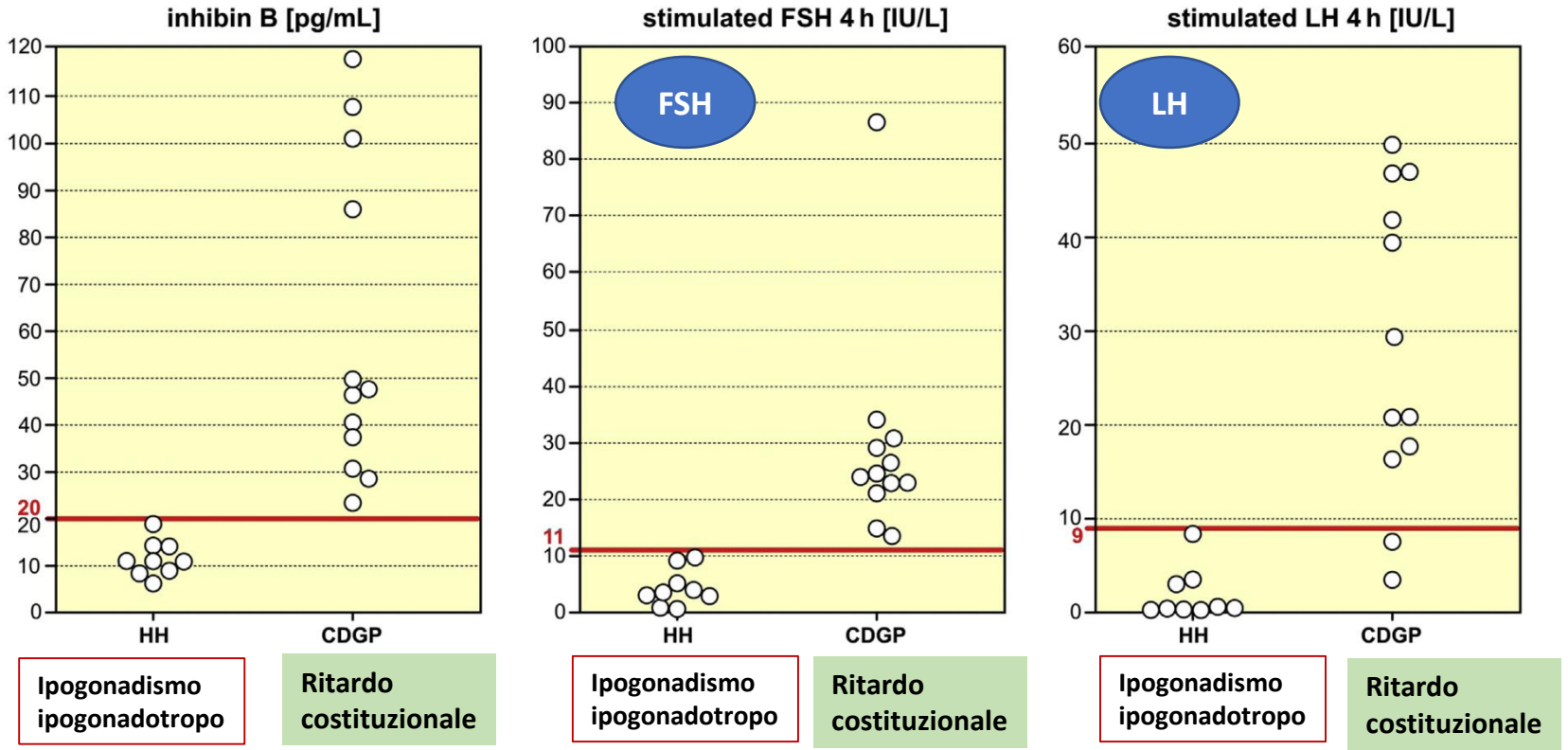
GnRH A test : migliore vs GnRH in diagnostica differenziale

- ⬆**LH / FSH dopo 3h (LH/FSH > 0,7 nelle femmine)**
  ⬆**E2 dopo 24h**

esclude diagnosi di ipogonadismo ipogonadotropo

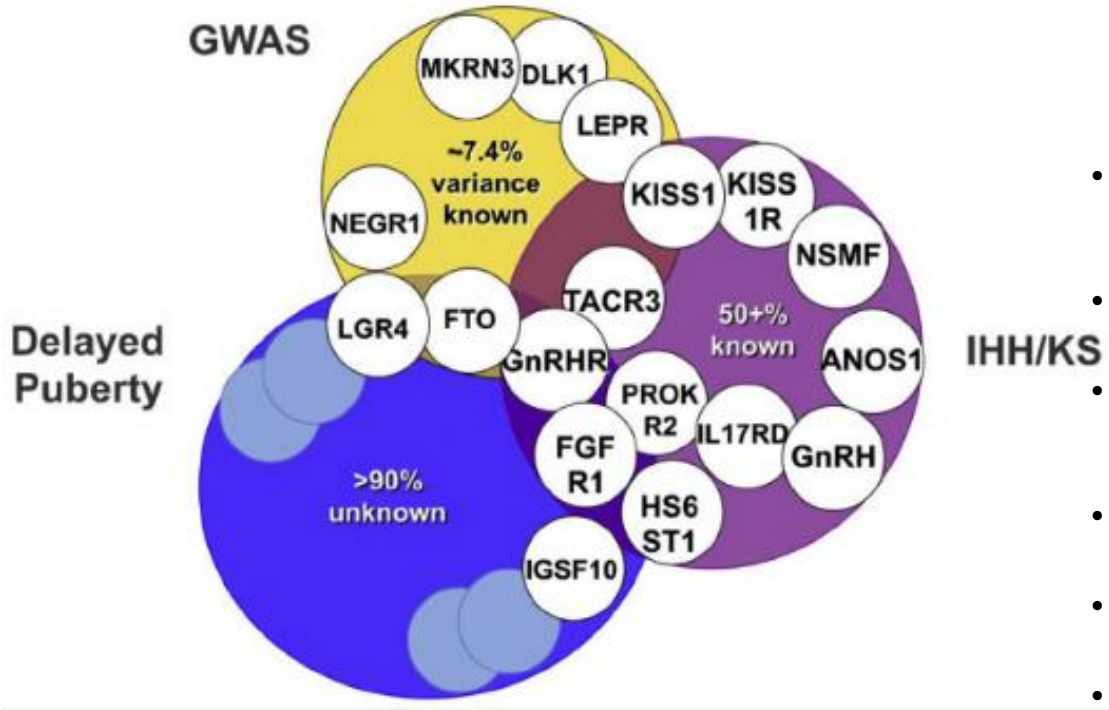
0.1 mg di triptorelina

Binder et A. 2015



Ipogonadismo ipogonadotropo	Ritardo costituzionale	Ipogonadismo ipogonadotropo	Ritardo costituzionale	Ipogonadismo ipogonadotropo	Ritardo costituzionale

Overlap between genetic regulation in the general population and extreme phenotypes.



- *GnRH and GnRH receptor (GnRHR) genes (2005,2011).*
- *Leptin or leptin receptor polymorphism (2008).*
- *Mutations in the IGF acid labile subunit (IGFALS) gene(2008).*
- *LIN28B gene (2010).*
- *Estrogen receptor α (ESR1) (2013).*
- *Genetic variants in FSHB and FSHR have been reported as modulators of FSH action genetic variation in promoters affecting FSH action(2014).*
- *MKRN3 (2015).*

Conditions of GnRH deficiency such as Idiopathic hypogonadotropic hypogonadism (IHH) and Kallmann Syndrome (KS)

Wide association studies in the general population (GWAS),

Genes underlying delayed puberty
S.R. Howard. 2018

Amenorrea primaria o secondaria

da ipogonadismo ipo-gonadotropo

FSH ⬇ ⬇

Normale riserva ovarica

AMH rilevabile

In relazione al tempo di insorgenza della patologia (pre-menarca / post menarca)

Gordon CM et Al 2017

Pituitary gland or stalk damage

Tumors and cysts [hypothalamic or pituitary tumor (hormone-secreting), craniopharyngioma, Rathke cleft cyst, other cysts, and tumors]

Infiltrative disorders (germinoma, autoimmune hypophysitis, sarcoidosis, hemochromatosis, tuberculosis, Langerhans cell histiocytosis, IgG4-related hypophysitis)

Irradiation, Infarction [apoplexy in pre-existing pituitary tumors, or following postpartum hemorrhage (Sheehan syndrome)]

Surgery Trauma

Amenorrea primaria o secondaria

da ipogonadismo ipo-gonadotropo secondario a

Patologia tiroidea

Patologia surrenalica

Forme funzionali

Gordon CM et Al 2017

Thyroid Hypothyroidism
or hyperthyroidism

Adrenals
Congenital adrenal hyperplasia
(select types)
Cushing syndrome
Addison disease (adrenal insufficiency)
Tumor (androgen-secreting)

Amenorrea primaria o secondaria

da ipogonadismo ipo-gonadotropo

su base funzionale

Eating disorders

Competitive athletics

Chronic disease

Mood disorders

Stress or psychiatric illness

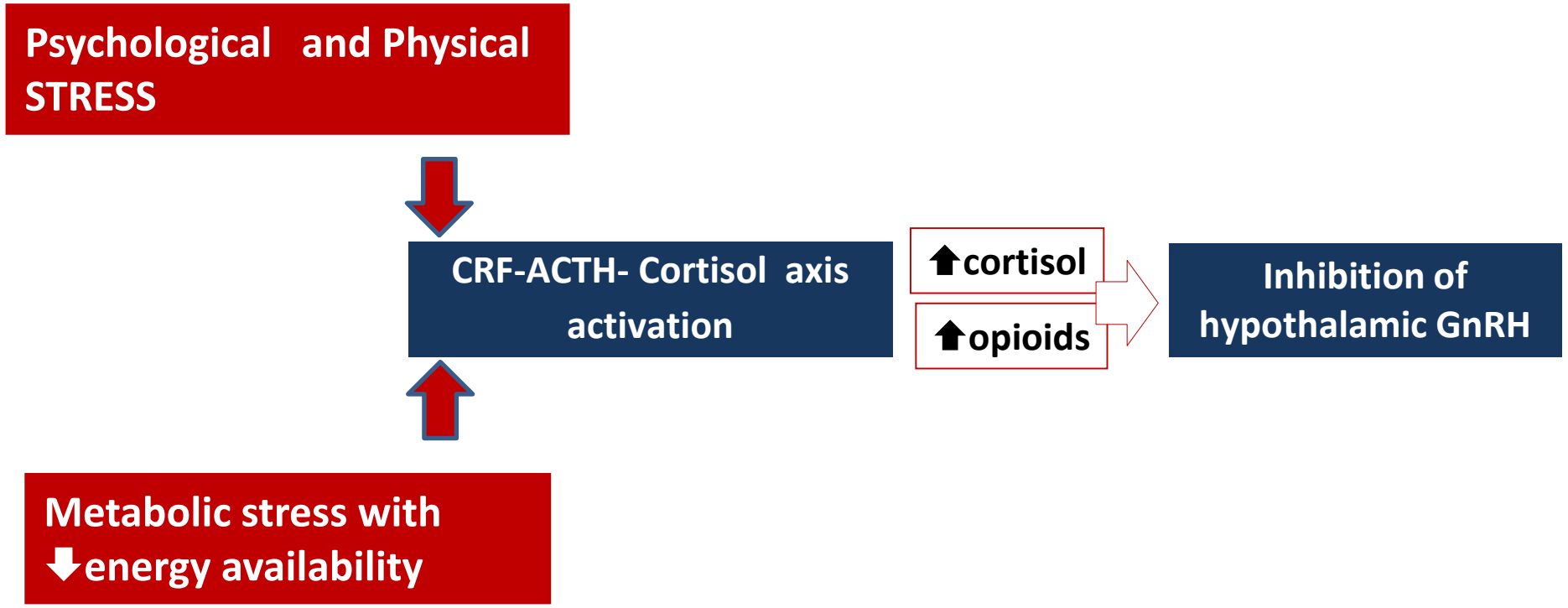
Drugs

Il concetto di **«stress»**

come combinazione di condizioni psicologiche, fisiche e metaboliche

Il rapporto tra nutrizione e mestruazione

Il grasso corporeo


Psychological and Physical STRESS
CRF-ACTH- Cortisol axis activation
⬆cortisol
⬆opioids
Inhibition of hypothalamic GnRH
Metabolic stress with ⬇energy availability

L'ipotalamo è il principale sensore dello stato nutrizionale, della disponibilità energetica e delle condizioni di stress

Informazioni dalla periferia sullo stato nutrizionale

Leptina

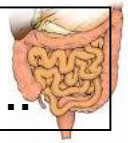
espressione riserve tessuto adiposo

Peptidi gastro-intestinali

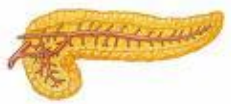
Ghrelina

espressione deficit nutrizionale

PYY
GLP-1 …



Insulina



Ruolo permissivo nel controllo dell'asse gonadotropinico

Irisina

«browning» of white fat, termogenesi omeostasi energetica

Risposte ipotalamiche alla bassa disponibilità energetica

Low energy availability = ⬇ Caloric and fat intake ± Exercise energy expenditure

HPA axis (hypothalamic pitutary , adrenal)	• ⬆ CRH , ⬆ ACTH , ⬆Cortisol • ⬆ Cortisol/DHEAS ratio
HPT axis (hypothalamic pituitary tyroid)	• ⬇ Free T3 .Normal or low TSH • Normal or low T4
GH – IGF1 axis	• ⬆GH , ⬇ IGF1 • Acquired GH resistance
HPG axis (hypothalamic – pituitary gonadal)	Impaired LH pulsatility Normal FSH levels ⬇ Estradiol ⬇ Testosterone

Normal levels of AMH

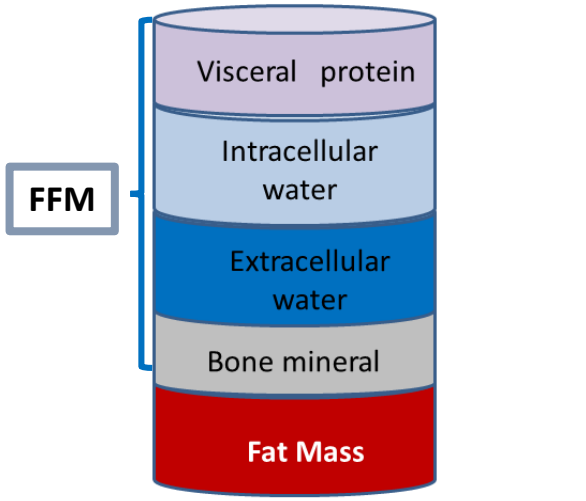
I marcatori delle amenorree ipotalamiche funzionali

Amenorrea da stress

Normale BMI

Normale massa grassa

Normale massa magra



Bioelectrical Impedance Analysis (BIA)

Valutare le condizioni di stress

Stress psicologico
Disagio economico
Relazioni familiari negative .
Avversità reali o attitudine negativa verso eventi del vivere quotidiano

⬆⇧ **Cortisolo**

- ⬆ **CRH**
- ⬆ **ACTH**
- ⬆ **Attività oppioidi endogeni**

⇓ **LH**

⬇ **Frequenza pulses**
(da 12 pulses / 24 ore a 7 pulses / 24 ore)

⬇ **E2**

Normali livelli FSH

Normali livelli AMH

I marcatori delle amenorree ipotalamiche funzionali

Normale BMI
⬇ massa grassa
Normale massa magra

Ridotto BMI
⬇ massa grassa
⬇ massa magra

Valutare
- Condizioni di stress
- Caloric intake
- Attività fisica

Valutare
possibilità di transizione
verso importante patologia
Comportamento alimentare

Valutare massa ossea

Valutare altre possibili
alterazioni somatiche

Amenorrea da inadeguato stato nutrizionale

⬇⬇ Leptin

⬆Ghrelin ⬆PYY

⬇Insulin

⬇ Free T3

⬆⬆ Cortisol

⬇DHEAS / Cortisol ratio

⬆⬆ GH ⬇ IGF1

⬆⬆ SHBG

⬇⬇ LH
⬇⬇ E2

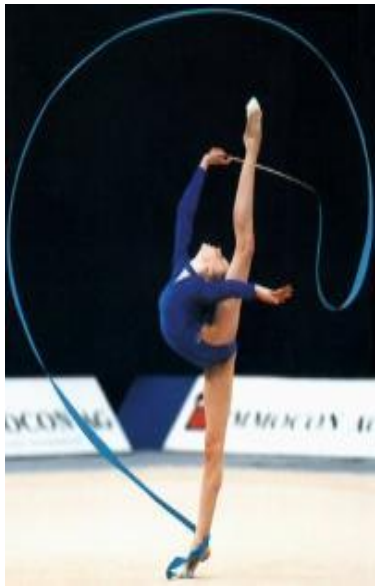
Normal AMH levels

I marcatori delle amenorree ipotalamiche funzionali

Amenorrea delle atlete

Prevalente in relazione ad attività fisiche che richiedono basso peso o Particolari aspetti estetici

Valutare possibile abuso di steroidi anabolizzanti



BMI non è generalmente Marker significativo

= / ⬇ BMI (generalmente modesta riduzione)

⬇ Massa grassa

⬆ **Massa magra**

⬇LH

⬇ E2

⬆⬆ **Cortisol**

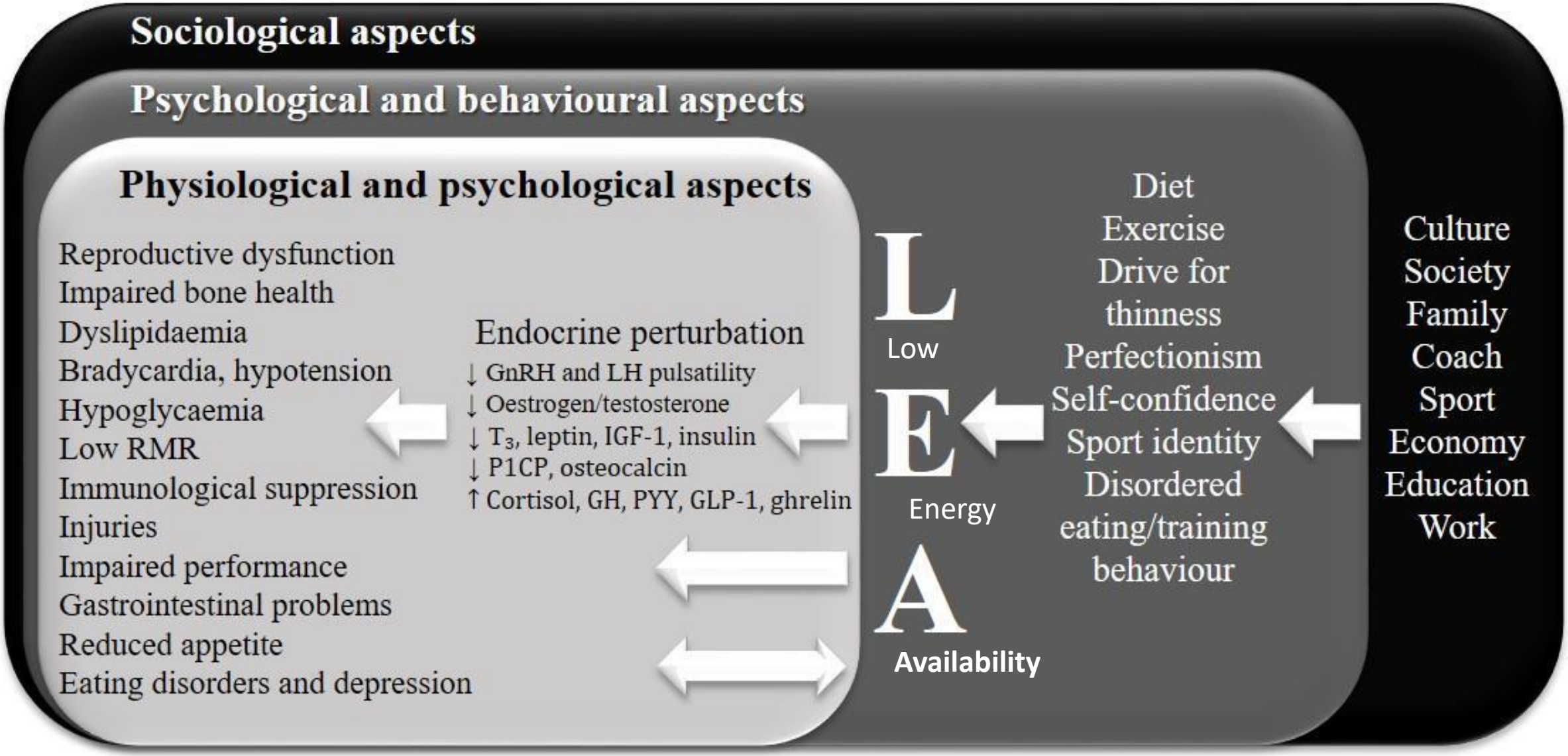
Se inadeguato apporto energetico

⬆ Ghrelina ⬇Leptina ⬇IGF1

⬇ Free T3

“Energy Availability in Athletics: Health, Performance and Physique”

Melin AK et Al 2018



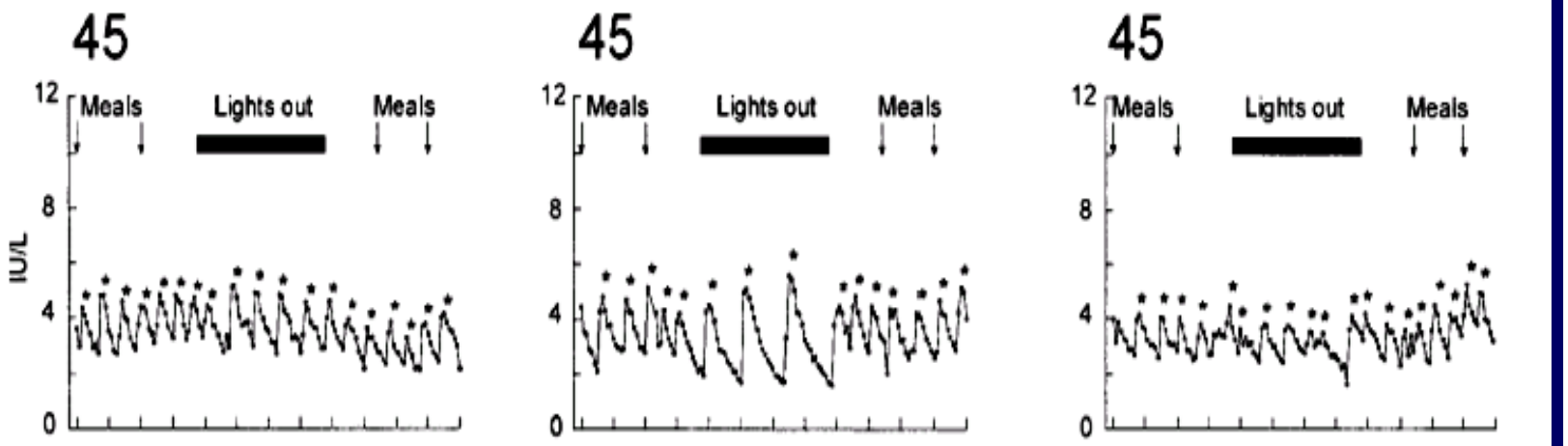
Fabbisogno energetico dell'atleta

Melin AK et Al 2018

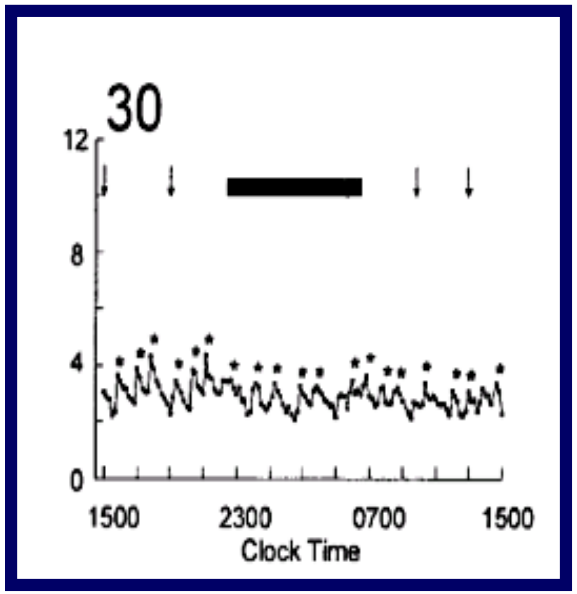
Energy availability	
> 45 kcal/kg FFM (females)	High EA For healthy weight gain or weight maintenance
≥ 45 kcal/kg FFM (females)	Optimal EA For weight maintenance providing adequate energy for all physiological functions. During periods with injury with alternative or rehabilitation training at low/moderate intensity ~ 1.5 h/day
30-45 kcal/kg FFM (females)	Subclinical LEA May be tolerated for short periods during a well-constructed weight loss program

Loucks & Thuma 2003

Luteinizing Hormone Pulsatility Is Disrupted at a Threshold of Energy Availability in Regularly Menstruating Women



Energy Availability (EA) = 45 Kcal /kg Lean Body Mass



Luteinizing hormone pulsatility is disrupted within 5 days, when EA is reduced below 30 kcal/kg FFM per day in subjects of gynecological age 5-8 years

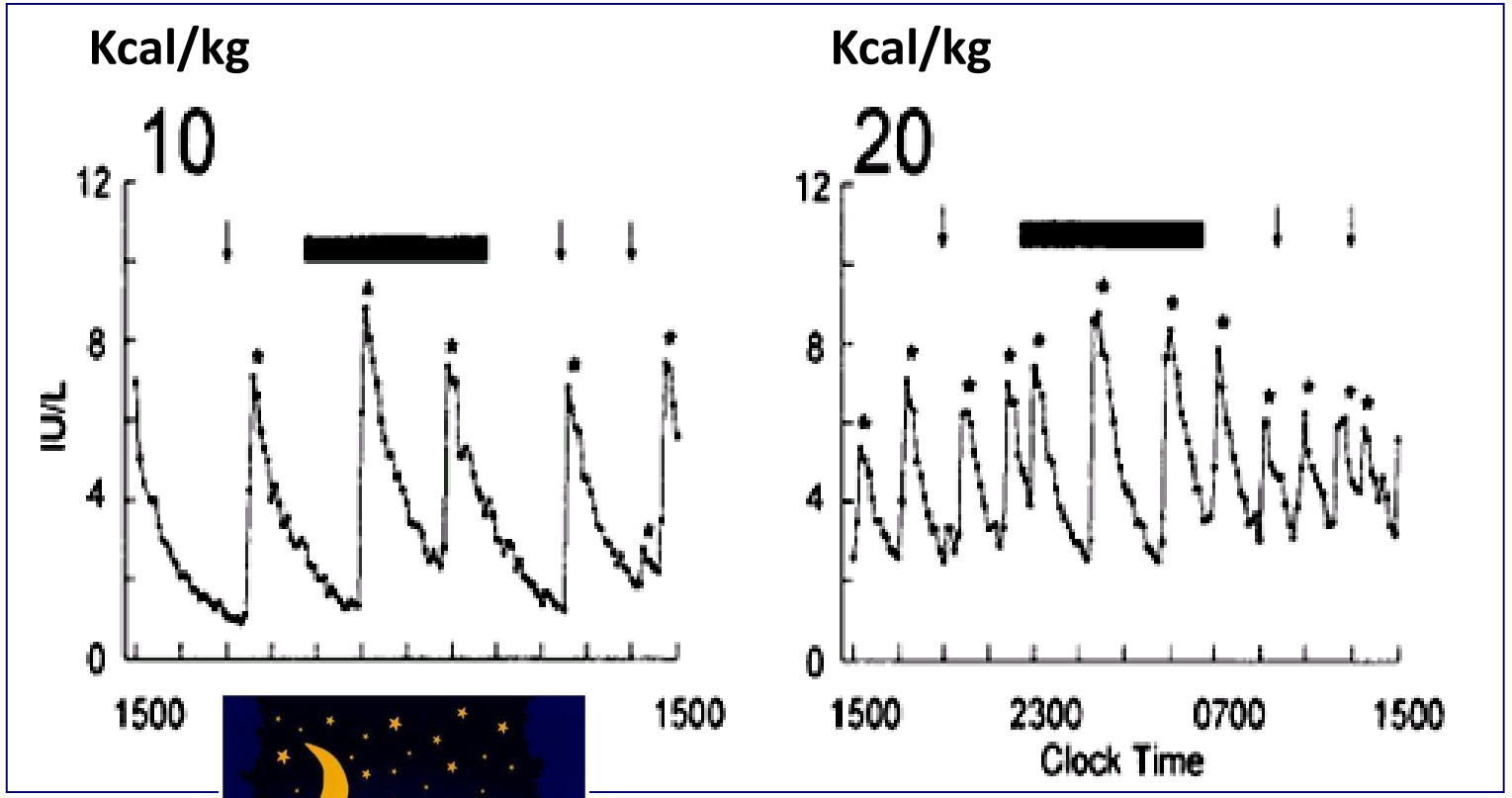
Leptin is substantially suppressed at EA= 30 kcal/kg FFM per day

Loucks & Thuma 2003

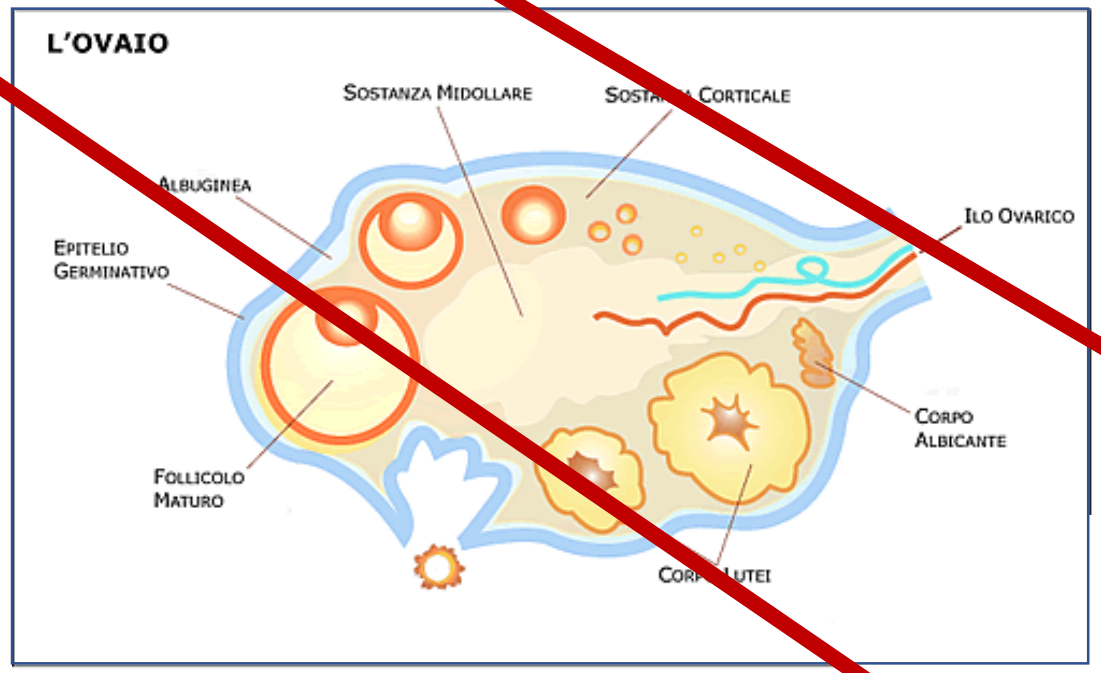
With reduction of energy availability a progressive decrease of LH pulsatility takes place

with regression to prepubertal pattern

and prevalent dismission during the night



Amenorrea da cause strettamente ovariche o da patologia interferente su funzione ovarica



Cause genetiche (20%) , cromosomiche (5%) familiarità

Cause iatrogene (chirurgia , chemioterapia ,radioterapia)

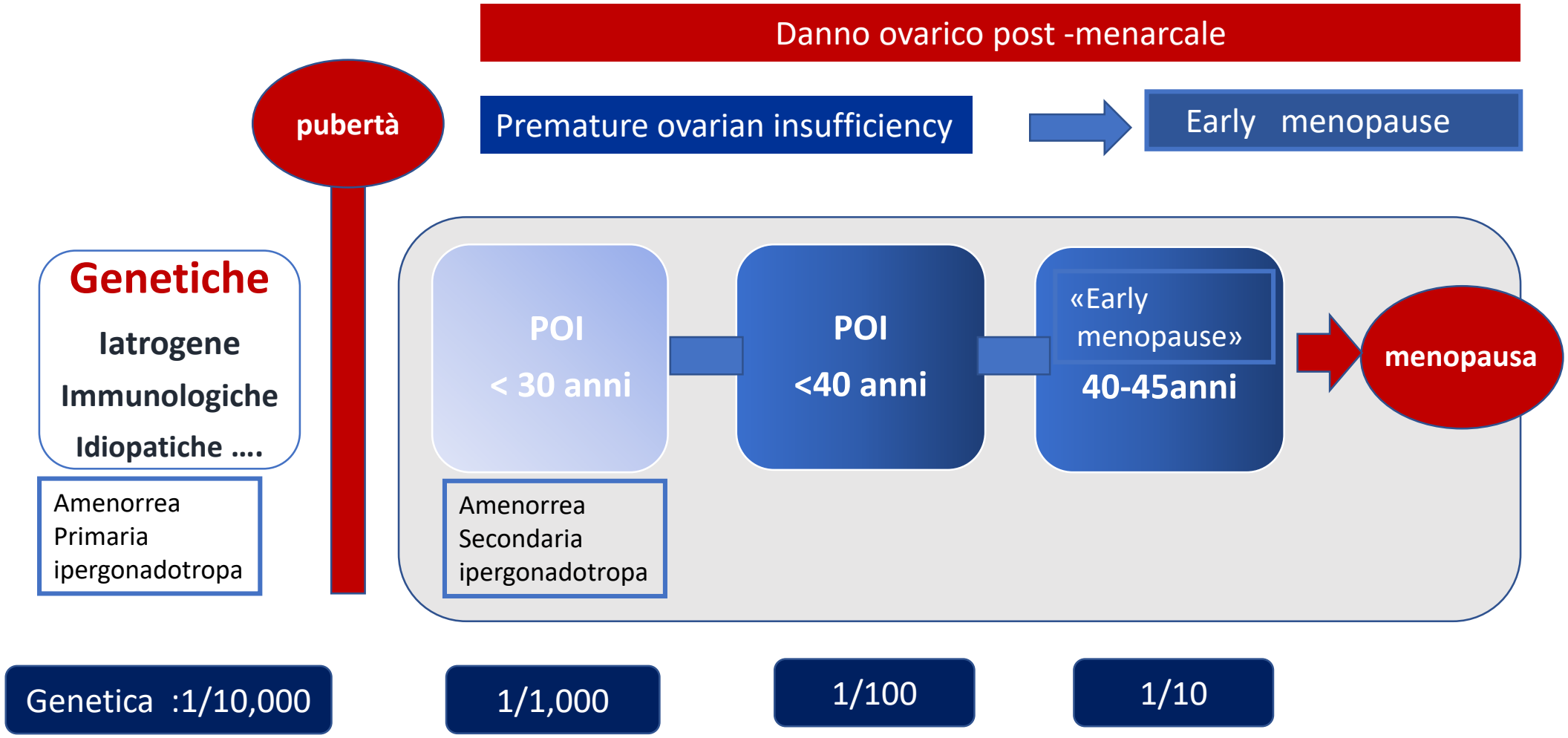
Cause immunologiche (10%)

Cause metaboliche (galattosemia , emocromatosi)

Idiopatiche (<50%)

L'amenorrea come espressione di danno ovarico → **è ipergonadotropa**

- **Primaria** — Danno ovarico Pre-menarcale
- **Secondaria** — Danno ovarico Post-menarcale


Danno ovarico post -menarcale
pubertà
Premature ovarian insufficiency
Early menopause
Genetiche
Iatrogene
Immunologiche
Idiopatiche ….
Amenorrea Primaria ipergonadotropa
POI
< 30 anni
POI
<40 anni
«Early menopause»
40-45anni
menopausa
Amenorrea Secondaria ipergonadotropa
Genetica :1/10,000
1/1,000
1/100
1/10

Vari termini sono stati usati per definire
questa alterazione della funzione ovarica in periodo post-menarcale

Primary ovarian Insufficiency (POI)

The term **«ovarian insufficiency»** suggests a possible resumption of ovarian follicular activity, even years after diagnosis, leading to pregnancy in some women

Transient ovarian failure
Premature ovarian dysfunction
Transient ovarian insufficiency
"fluctuating POI"
Occult ovarian failure
Incipient ovarian failure

Premature ovarian failure (POF)

The term **«ovarian failure»** suggests a definitive loss of ovarian follicular activity

Early menopause

Targeting therapy

Pre-pubertal onset

Primary

Hyper-gonadotropic

Amenorrhea

- Induction of secondary sexual characteristics (SSC)
- Genital tract maturation
- Peak bone mass achievement
- CVD , neurological health
- Psychological support

Post-pubertal onset

Secondary

Hyper-gonadotropic

Amenorrhea

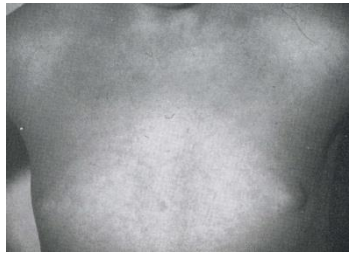
- Recovery of estrogen levels and menstrual function

Induction of secondary sexual characteristics (SSC)

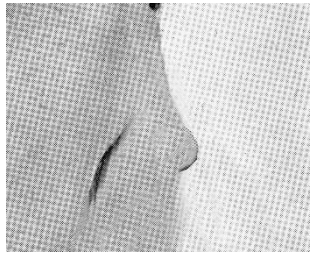
- Genital tract maturation
- Peak bone mass achievement
- CVD , neurological health
- Psychological support

The primary criterion for successful pubertal induction was to achieve staging B4 within 2 yrs

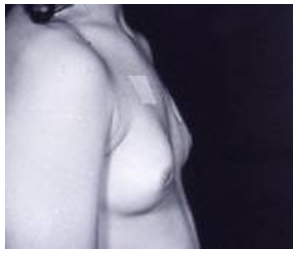
Tanner stages



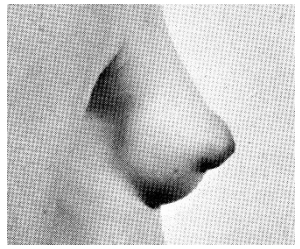
stage I



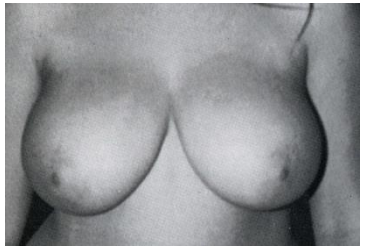
stage II



stage III

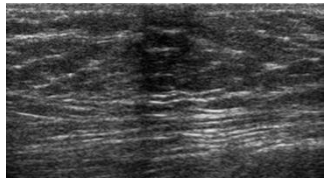


stage IV

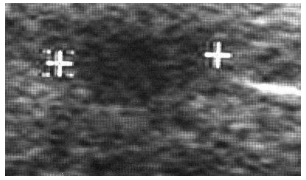


stage V

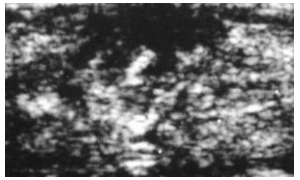
US evaluation of mammary gland development during puberty



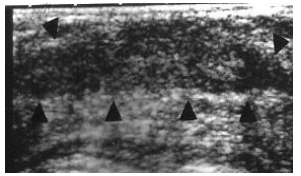
stage I



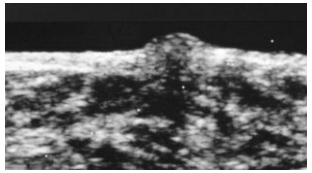
stage II



stage III



stage IV



stage V

Induction of secondary sexual characteristics (SSC)

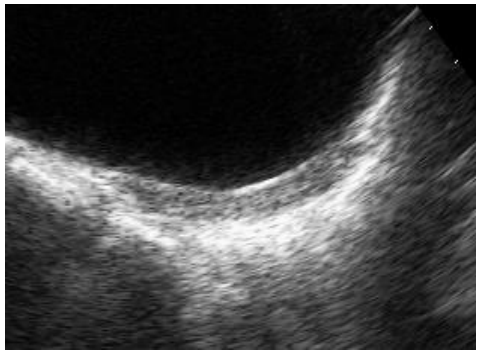
Genital tract maturation

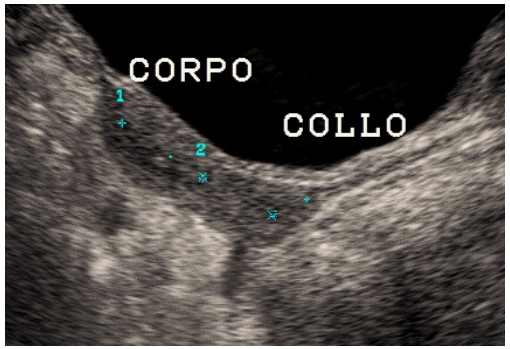
Peak bone mass achievement

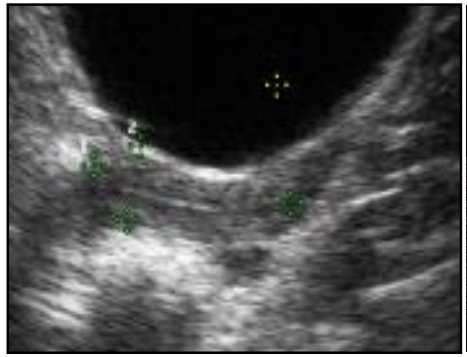
CVD , neurological health

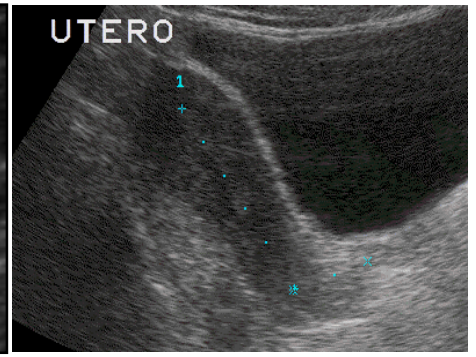
Psychological support

US evaluation of uterine development during therapy

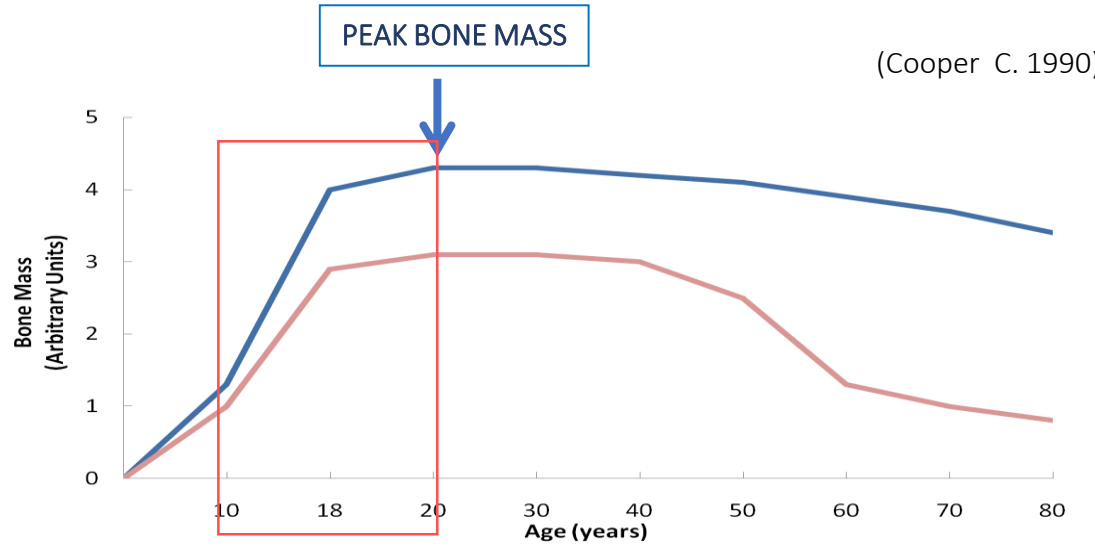








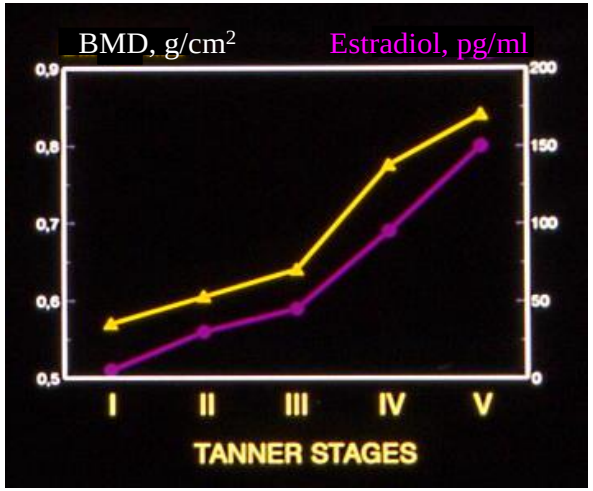
- Induction of secondary sexual characteristics (SSC)
- Genital tract maturation
- **Peak bone mass achievement**
- CVD , neurological health
- Psychological support



(Cooper C. 1990)

Changes in bone mass with age

Genetic factors | Ethnic factors | Nutrition | Physical activity | **Hormonal effects**



- Peak bone mass achievement
- Dosaggi adeguati
- Migliore la somministrazione TD

Terapia per induzione
Iter puberale

Amenorrea
Primaria
ipergonadotropa

Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 10–25.

2007

Davenport M.L. Approach to the Patient with TurnerSyndrome JCEM April 2010, 95(4):1487–1495

2008

2010

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

2017

European Society of Endocrinology

Pre-pubertal onset

Primary

Hyper-gonadotropic

Amenorrhea

- Induction of secondary sexual characteristics (SSC)
- Genital tract maturation
- Peak bone mass achievement
- CVD , neurological health
- Psychological support

Targeting therapy

Post-pubertal onset

Secondary

Hyper-gonadotropic

Amenorrhea

- Recovery of estrogen levels and menstrual function

Terapia POI / POF

1. **POI is a pathological condition**

2. The approach to the effects of POI on a woman's health must be evaluated differently from those of natural menopause

3. HRT is an efficacious therapy in POI patients due to its short and long term effects on POI

3. HRT is indicated in the prevention of OP, CVD genito-urinary syndrome treatment and improvement of quality of life

5. **HRT not bifosfonets , should be the first treatment for POI patients with osteoporosis**

6. HRT must be administered in physiological hormone doses , but monitoring of E2 levels is not recommended

7 .HRT is preferable to EP
(to be considered in case of need for a contraceptive)

8. Women who want a contraceptive without EP should use E2 TTS + IUD-LNG vs POP

9. **HRT must be continued until the patient reaches the age of physiological menopause**

Flores VA e Pal L,
Clin Obstet Gynecol 2018;

Committee on Gynecologic Practice,
Committee Opinion 2017

Valutazione BMD (DEXA) alla diagnosi di POI /POF in tutte le donne , in particolare se presenti fattori di rischio per osteoporosi

Se **normale BMD** e adeguata HRT via sistemica, la ripetizione della DEXA ha scarso valore

Se **diagnosi di osteoporosi** e adeguata terapia
la ripetizione della DEXA dovrebbe essere eseguita entro 5 anni

Se ↓BMD rivalutare terapia ; consulenza da specialista in osteoporosi può essere appropriata

ESHRE Guideline : management of women with premature ovarian insufficiency

Hum Reprod. 2016
Webber L, Davies M , Anderson R et Al

2016

Valutazione BMD (DEXA) alla diagnosi di POI /POF

Ripetere la valutazione in relazione a valore di BMD iniziale
fattori di rischio per osteoporosi
compliance per la terapia

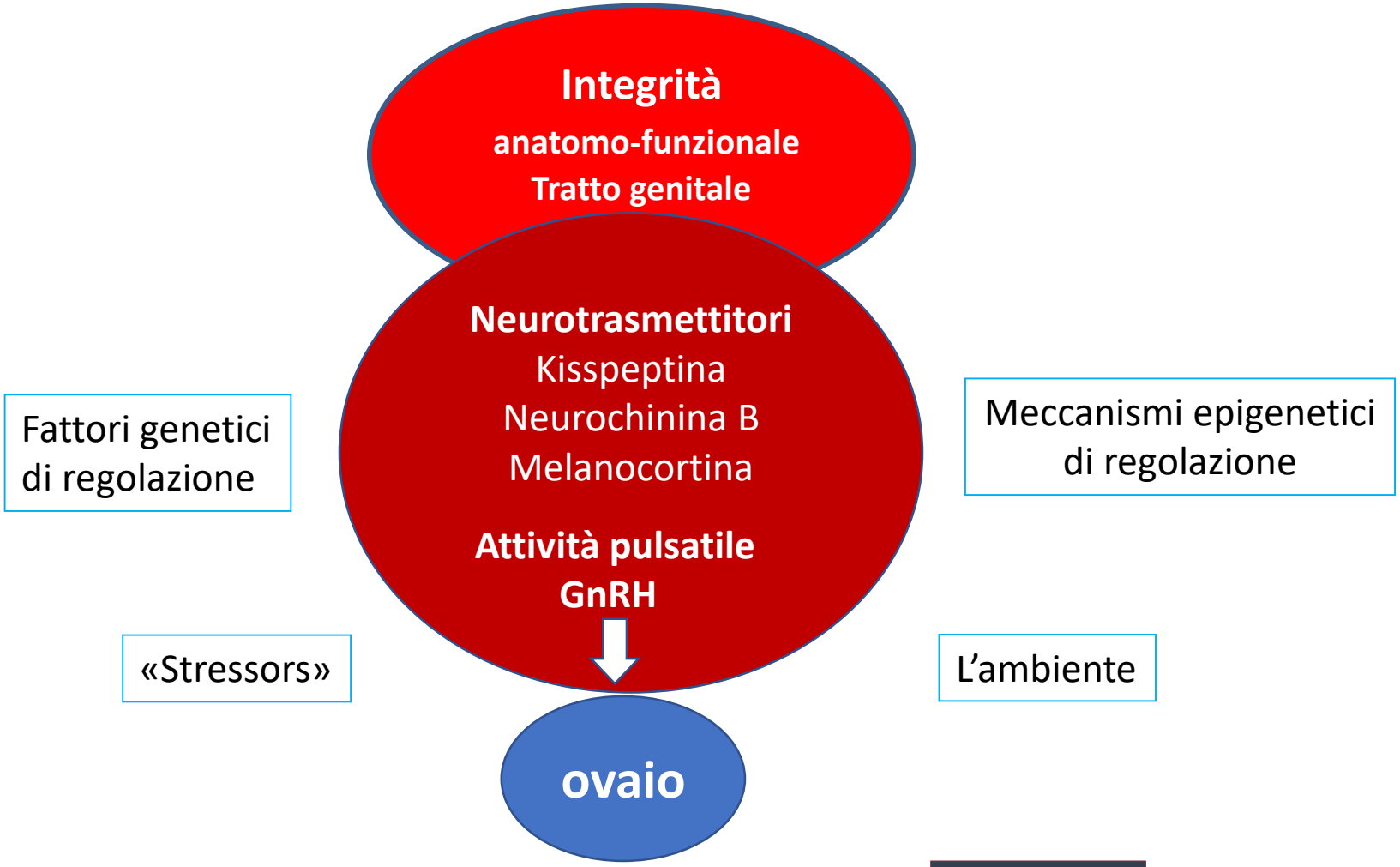
HRT e COC come terapia ; HRT può essere migliore per massa ossea

The British Menopause Society and Women's Health Concern recommendations on the management of women with premature ovarian insufficiency

2017

Haitham Hamoda;[1] on behalf of The British Menopause Society and Women's Health Concern

La funzione mestruale



La funzione riproduttiva