QUELLO CHE L'ENDOCRINOLOGO DEVE SAPERE DELLA TOS IN MENOPAUSA

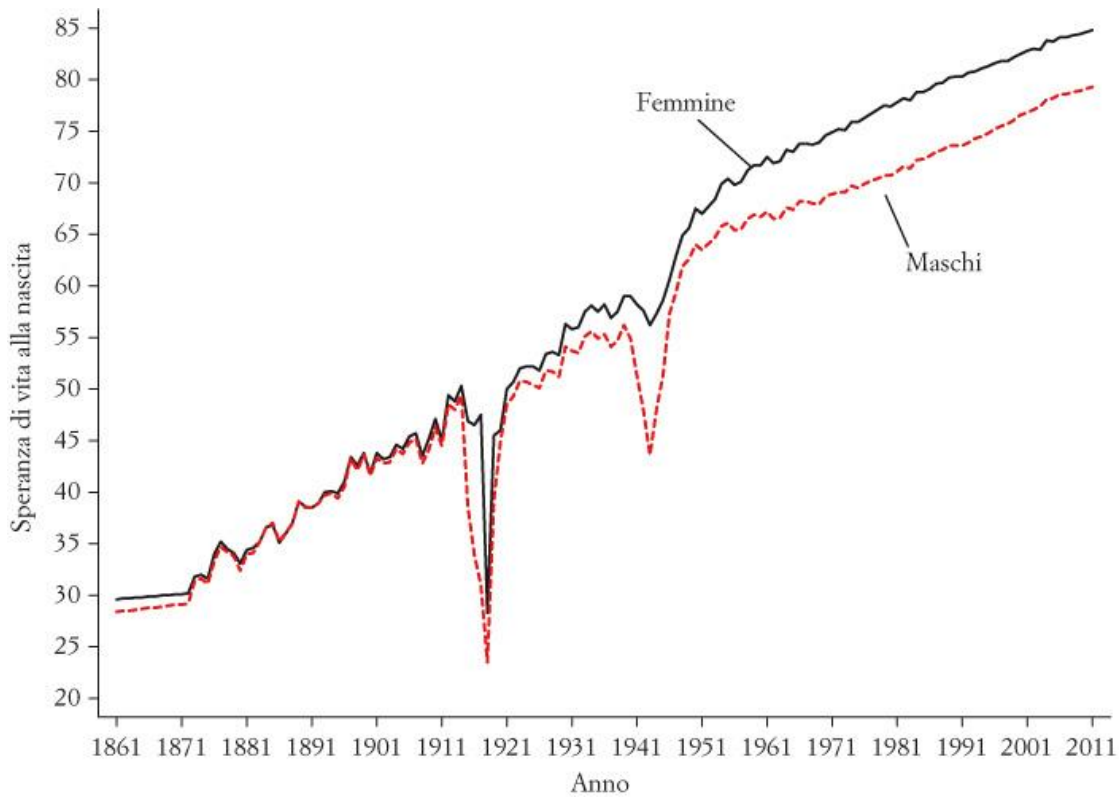
Rossella E. Nappi

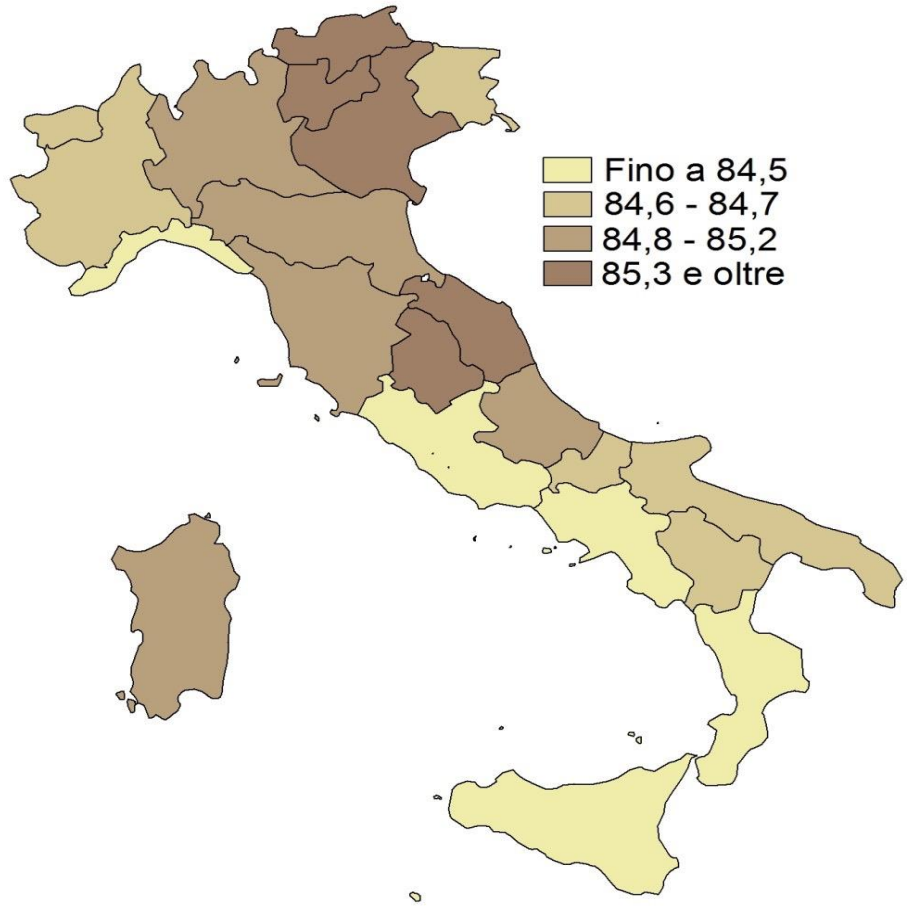
Centro per la Procreazione Medicalmente Assistita, Endocrinologia Ginecologica e della Menopausa - IRCCS «Policlinico S. Matteo»

Unità di Clinica Ostetrica, Ginecologica e della Riproduzione Umana, Dipartimento di Scienze Cliniche, Chirurgiche, Diagnostiche e Pediatriche, Università degli Studi di Pavia

Membro del Comitato Direttivo dell'International Menopause Society (IMS)

85.1 years: life expectancy in Italian women





14 millions are women > 49 years (6.5 millions between 50- 65 years) out of 31.2 millions

<u>50-51 years</u>: mean age at menopause

ISTAT, Noi Italia 2017

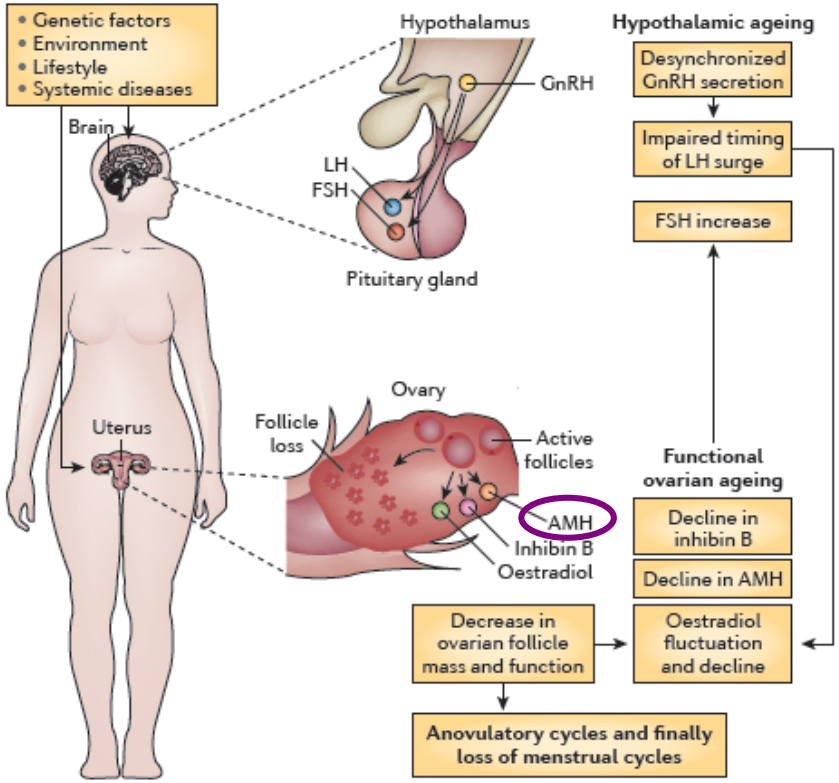
Women's Successful Ageing is also our Responsibility as HCPs

- Genes
- Life-Style
- Environment
- Health Care
- Socio-Economic Factor

RE Nappi, 2009

Reproductive Senescence

Chronologic Variability



Neuroendocrine Instability

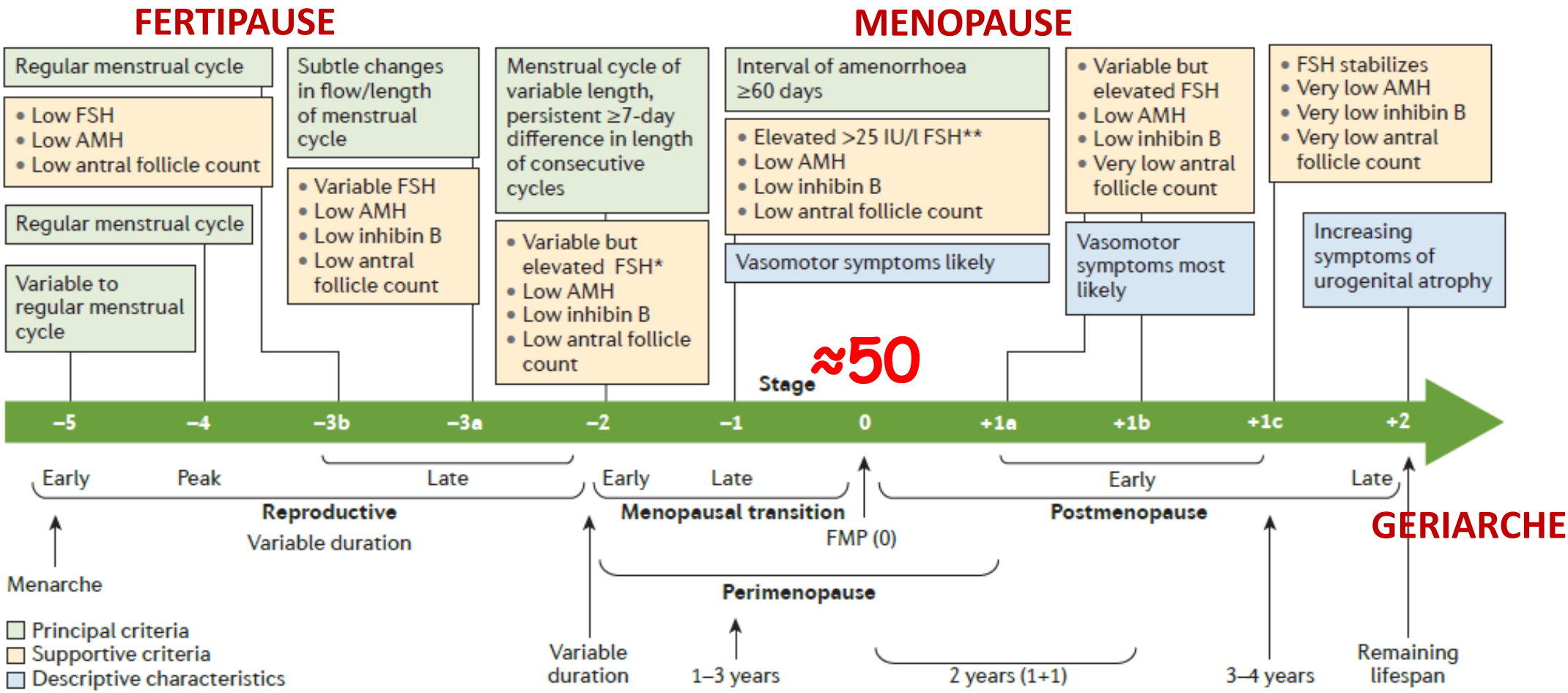
Ovarian Dependency

Figure 3 | **Menopausal loss of ovarian function.** Several processes contribute to declining ovarian function and the development of menopause including: hypothalamic and functional ovarian ageing; environmental, genetic and lifestyle factors; and systemic diseases. Hypothalamic ageing leads to desynchronized gonadotropin-releasing hormone (GnRH) production and an impaired surge of luteinizing hormone (LH) release from the pituitary gland. These central nervous system changes, together with ovarian ageing, impair ovarian follicle maturation, hormone production (inhibin B, anti-Müllerian hormone (AMH) and oestradiol) and ovulation. This leads to cycle irregularities and follicle-stimulating hormone (FSH) upregulation.

Davis et al, 2015

Menopausal Stages

Reproductive senescence is a very long journey!

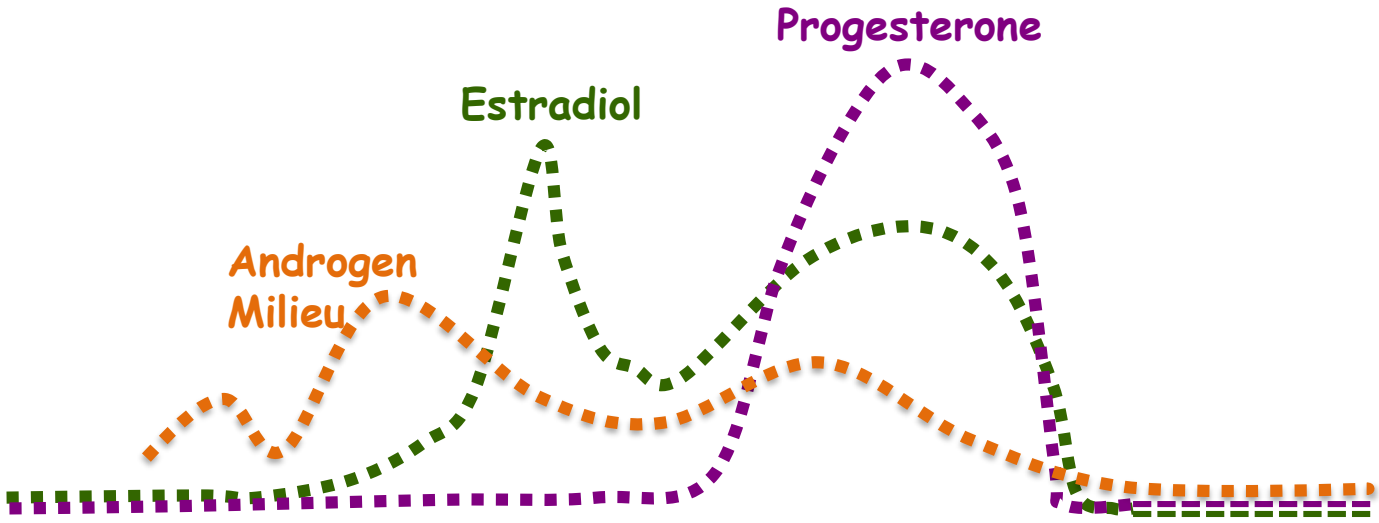


The Hallmark is the change of menstrual cycle characteristics

Davis et al, 2015

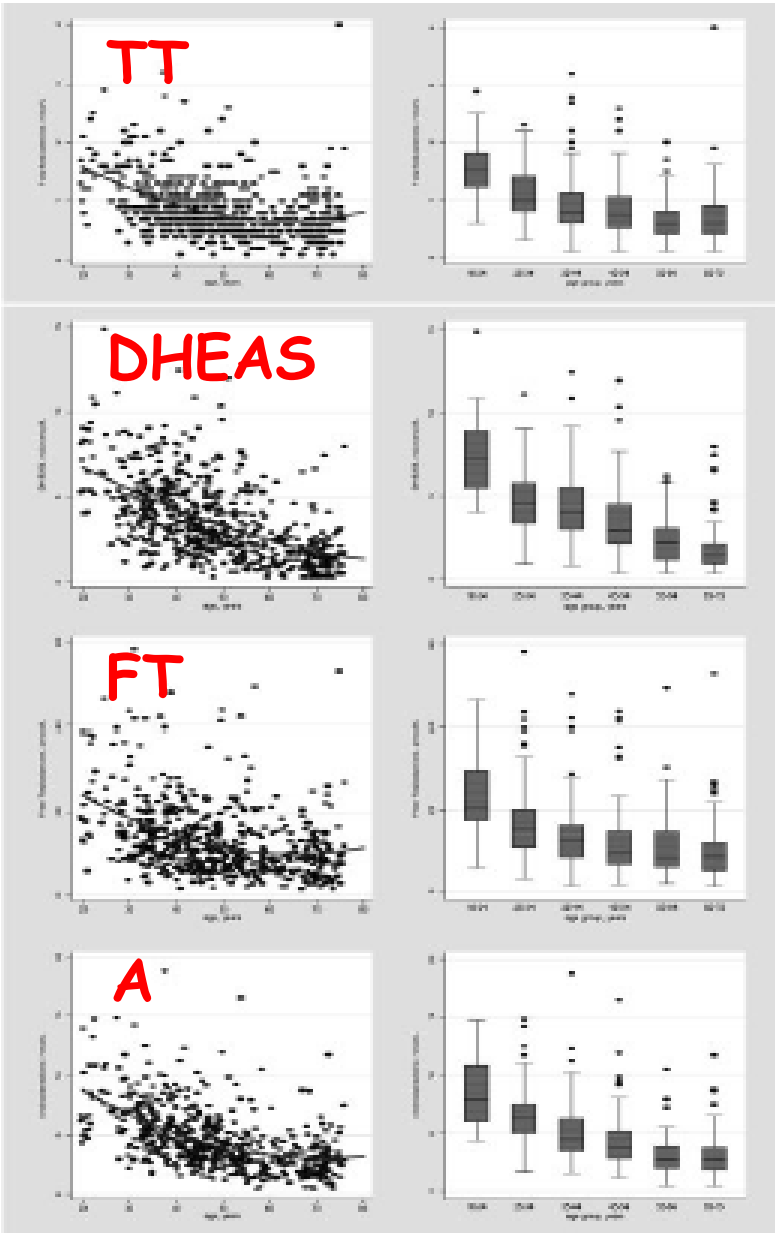
Hormonal Milieu in Women

SEX HORMONES [pg/mL]	FERTILE AGE	NATURAL MENOPAUSE	SURGICAL MENOPAUSE
Estradiol	50-300	10-15	10
Progesterone	50-10.000	500	50
Testosterone	400	290	110
Androstenedione	1.900	1.000	700
DHEA	5.000	2.000	1.800
DHEAS	3.000.000	1.000.000	1.000.000



Lobo RA, 2001

ANDROGENS & AGING IN WOMEN

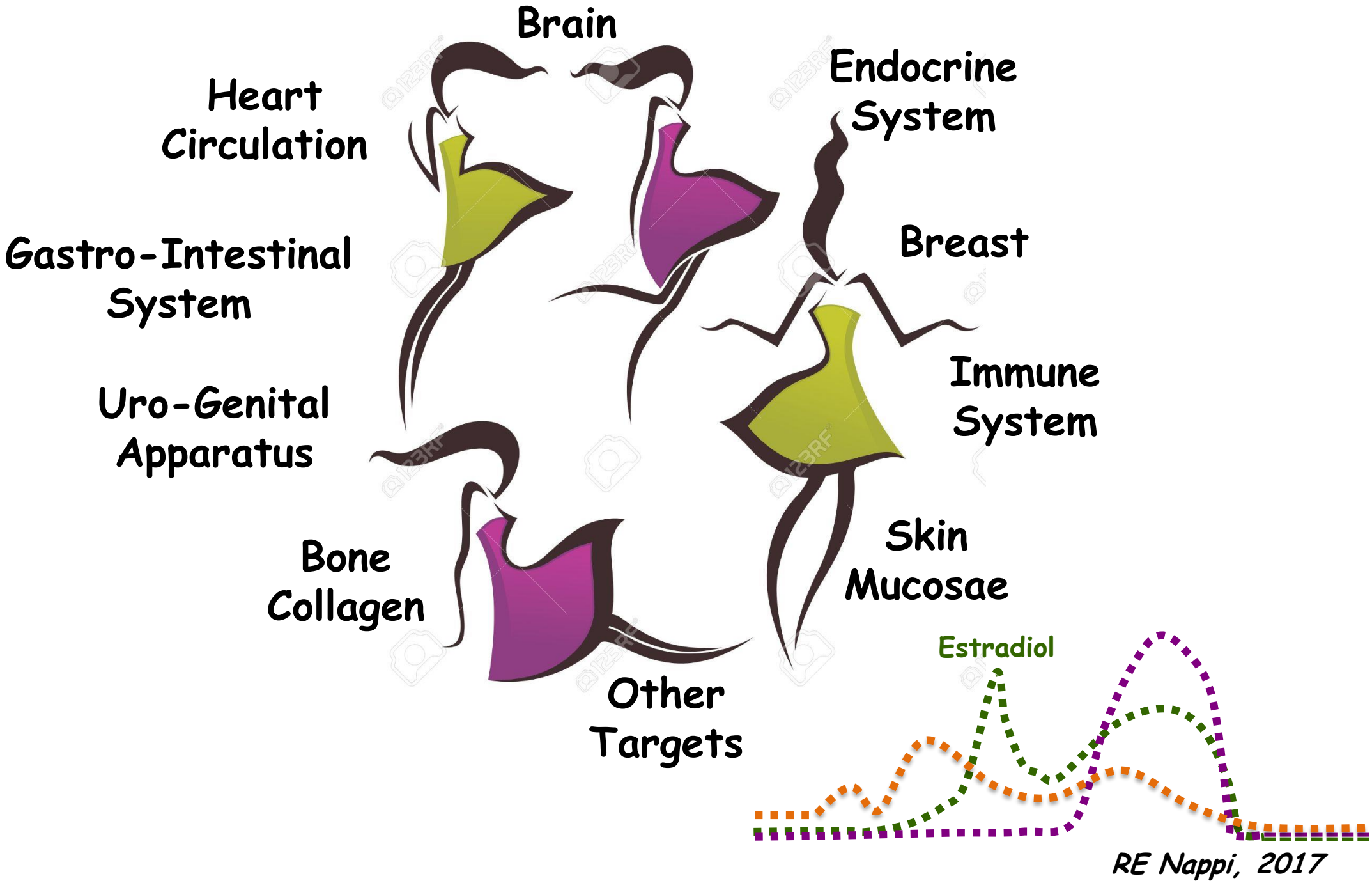


DIAGNOSIS of ANDROGEN INSUFFICIENCY is based on

- Symptoms (Type, Severity…)
- Circumstances (Premature Menopause…)
- ANDROGEN DECLINE IS RELATED TO AGE AND NOT TO NATURAL MENOPAUSE!!!
- DHEAS LEVELS SEEM ASSOCIATED TO WELL-BEING IN WOMEN AGED 45 YEARS OR OLDER

Simon, 2004;
Santoro et al, 2005;
Davis et al, 2005;
Davison et al, 2005

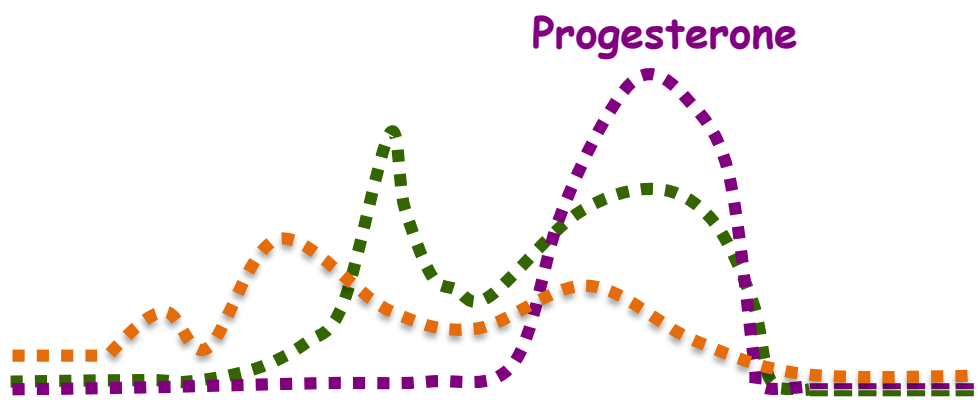
Estrogens – the Feminizing Hormones



Not only Estrogens – Impact of Progesterone on Women's Health

- **Progesterone is NOT a feminizing hormone but its major role is to modulate/antagonize Estrogens. It is a crucial metabolic intermediate in the production of other steroids (androgens, corticosteroids) and plays an important role in brain function as a neurosteroid.**
  - **Ovarian, Endometrial and Breast Physio-Pathology**
  - **Pregnancy, Parturition and Lactation**
  - **Neuroprotection**
  - **Muscle Contractility**
  - **Immunoregulation**
  - **Energy Balance**
  - **Metabolism**
  - **Vascular Reactivity**
  - **Sexual Behavior**
  - ***Many other effects…***

❖ ***Progestogens may have different impact according to their chemical nature and similarity to natural progesterone***



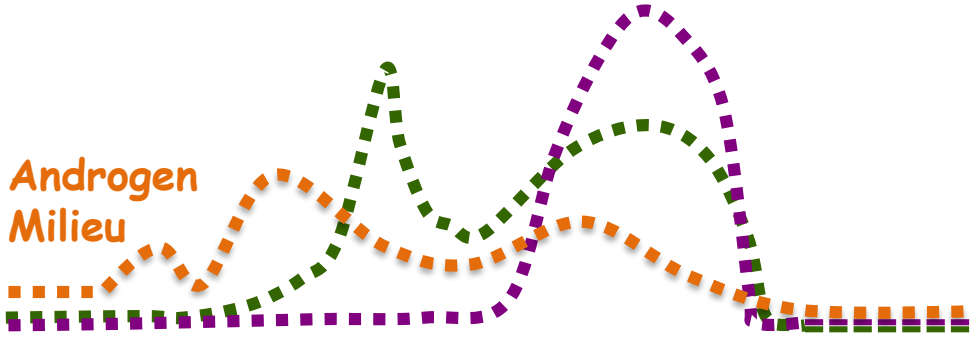
RE Nappi, 2017

Not only Estrogens – Impact of Androgens on Women's Health

- SEXUAL FUNCTION
- MOOD
- ENERGY
- COGNITION
- SENSE OF WELL-BEING
- BONE HEALTH
- MUSCLE MASS
- BODY COMPOSITION
- SKIN APPEARANCE
- *breasts, cardio-vascular function, reproduction, immune system…*

Diagnosis should be based on

- Symptoms (Type, Severity..)
- Circumstances (Low Functional Ovarian Reserve/Premature Menopause…)



Cameron & Braunstein, 2004

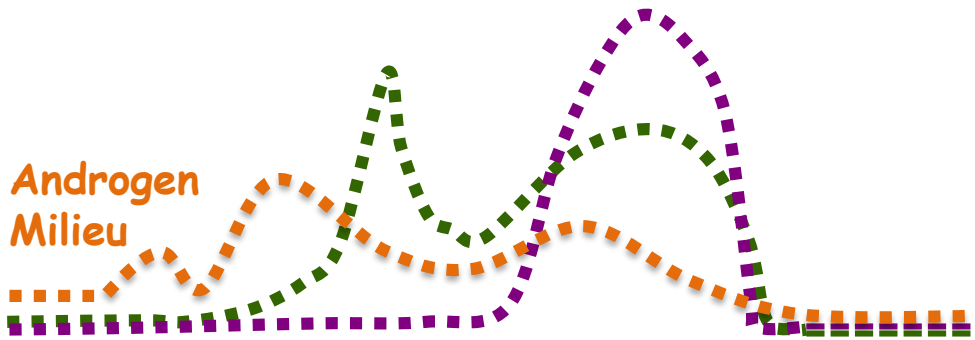
Low Testosterone in Women - Symptoms

REDUCED

- Sex Motivation
- Sex Fantasy
- Sex Enjoyment
- Sex Arousal
- Genital Vasocongestion
- Pubic Hair
- Bone Mass
- Muscle Mass Quality of Life (Mood, Affect, Energy)

MORE FREQUENT

- Vasomotor Symptoms
- Insomnia
- Depression
- Headache



GA Bachmann, 2002

Low Testosterone in Women - Circumstances

Physiological

- Aging

Pathophysiologic

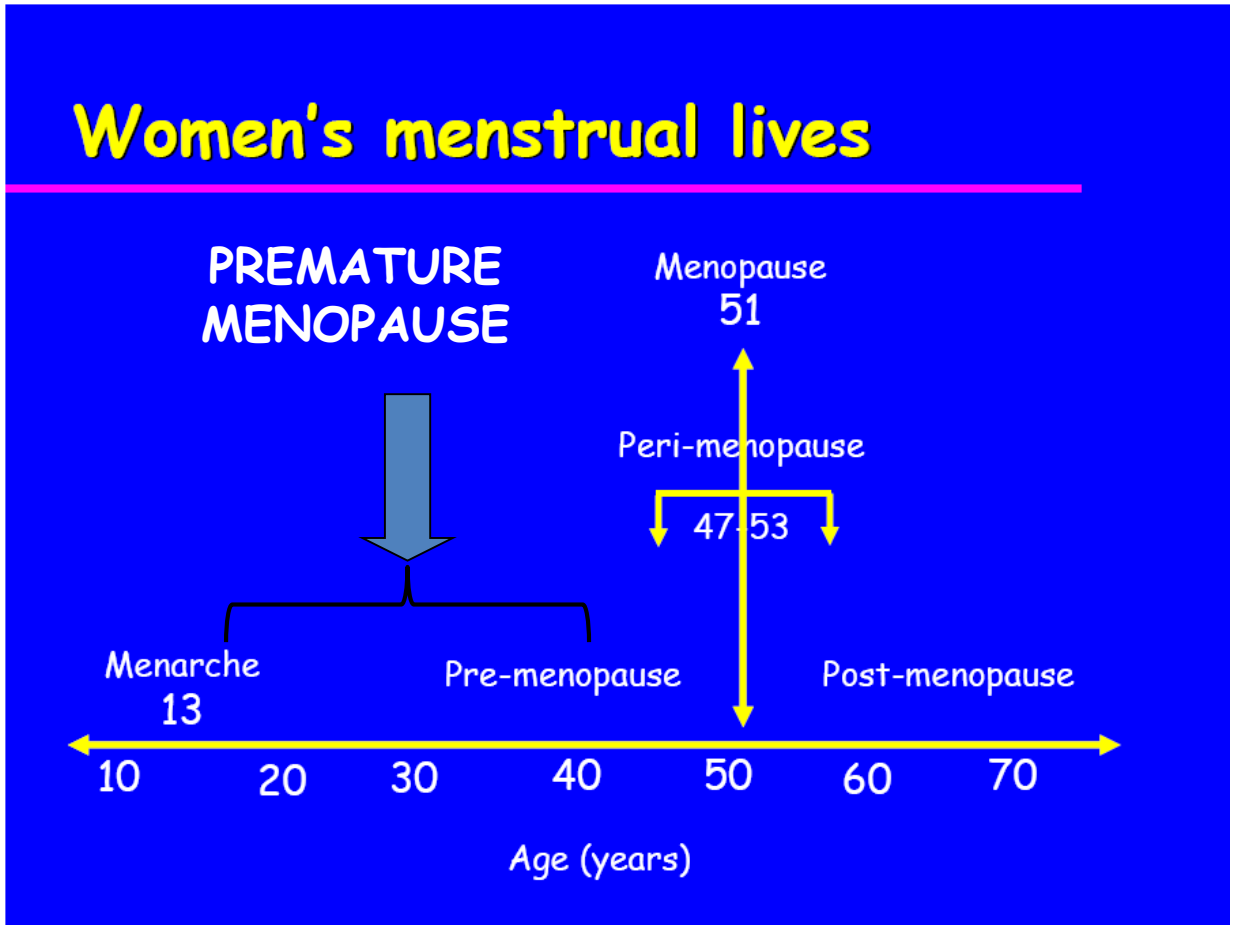
- Primary ovarian insufficiency (all causes)
- Adrenal insufficiency
- Panhypopituitarism
- Hyperprolactinemia
- Hypothalamic amenorrhea

Iatrogenic

- Hysterectomy
- Bilateral oophorectomy
- Antiandrogen therapy (eg, spironolactone, cyproterone acetate)
- Chemical ovarian suppression (eg, GnRH analogs)
- Chemotherapy
- Radiation to pelvis
- Oral estrogen
- Glucocorticosteroid therapy

Davis et al, 2016

Premature Menopause – an Early Event in the Ageing Process

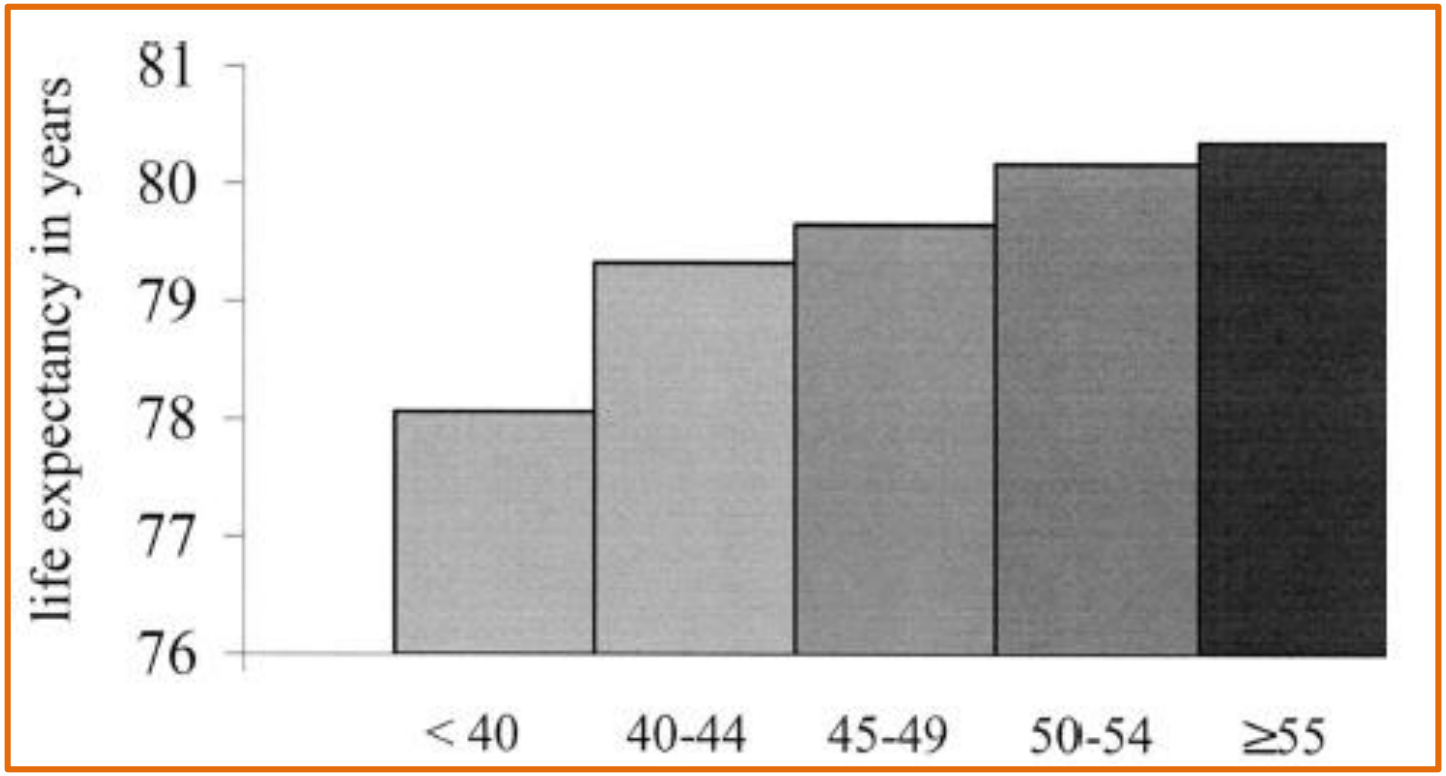


- **Population prevalence of 1% (varies by ethnicity) before the age of 40 yrs**

Pol & Santoro, 2002; Luborsky et al, 2003

Age at Menopause, Cause-Specific Mortality and Total Life Expectancy

- Data from a breast cancer screening cohort comprising 12,134 Dutch postmenopausal women (age: 57.4±4.3) followed for an average of 17 years (age at menopause: 49±4.5).



- Age-adjusted mortality is reduced 2% with each increasing year of age at menopause. In particular, ischemic heart disease mortality is 2% lower. Although the risk of death from uterine or ovarian cancer is increased by 5%, the net effect of a later menopause is an increased lifespan.
- Age at menopause was not strongly associated with the risk of death from breast cancer (1.02 per year; 0.97–1.06).

Ossewaarde et al, 2005

Ages at Menarche and Menopause and Reproductive Lifespan as Predictors of Exceptional Longevity in Women

- **A prospective study of postmenopausal women from the WHI with an average age of 74.7 years (range, 69-81 yrs) at baseline. Out of 16,251 women, 8,892 (55%) survived to age 90.**

TABLE 3. *Associations of reproductive characteristics with survival to age 90 among postmenopausal women*

	No./total (%) survived to 90	Age-adjusted OR (95% CI)	P_{trend}	Multivariable-adjusted OR (95% CI)	P_{trend}
Age at menarche, y[a]					
<12	1,415/2,708 (52.3)	1 [Reference]		1 [Reference]	
≥12	7,477/13,543 (55.2)	1.11 (1.02-1.21)	0.61	1.09 (1.00-1.19)	0.77
Age at menopause, y[a]					
<40	609/1,251 (48.7)	1 [Reference]		1 [Reference]	
40-44	1,099/2,107 (52.2)	1.13 (0.98-1.31)		1.09 (0.94-1.27)	
45-49	1,878/3,443 (54.6)	1.24 (1.09-1.41)	<0.001	1.13 (0.98-1.30)	0.01
50-54	3,554/6,335 (56.1)	1.32 (1.17-1.50)		1.19 (1.04-1.36)	
≥55	1,752/3,115 (56.2)	1.34 (1.17-1.53)		1.18 (1.02-1.36)	
Age at natural menopause, y[a]					
<40	494/1,009 (49.0)	1 [Reference]		1 [Reference]	
40-44	995/1,910 (52.1)	1.12 (0.96-1.31)		1.06 (0.90-1.25)	
45-49	1,721/3,168 (54.3)	1.22 (1.05-1.41)	<0.001	1.11 (0.95-1.29)	0.02
50-54	3,450/6,159 (56.0)	1.31 (1.14-1.50)		1.18 (1.02-1.36)	
≥55	1,676/2,990 (56.1)	1.32 (1.14-1.53)		1.16 (0.99-1.36)	
Age at surgical menopause, y[a]					
<40	115/242 (47.5)	1 [Reference]		1 [Reference]	
40-44	104/197 (52.8)	1.23 (0.83-1.82)		1.35 (0.88-2.08)	
45-49	157/275 (57.1)	1.46 (1.02-2.09)	0.02	1.33 (0.90-1.98)	0.11
50-54	104/176 (59.1)	1.59 (1.06-2.38)		1.50 (0.96-2.34)	
≥55	76/125 (60.8)	1.50 (0.96-2.36)		1.43 (0.86-2.38)	
Reproductive lifespan, y[b]					
<33	2,127/4,141 (51.4)	1 [Reference]		1 [Reference]	
33-37	2,499/4,514 (55.4)	1.17 (1.07-1.27)		1.11 (1.01-1.21)	
38-40	2,068/3,669 (56.4)	1.22 (1.12-1.34)	<0.001	1.17 (1.06-1.29)	0.008
>40	2,198/3,927 (56.0)	1.21 (1.11-1.33)		1.13 (1.03-1.25)	

- **The odds of longevity were 13% (OR 1.13; 95% CI, 1.03-1.25) higher in women with more than 40 compared with less than 33 reproductive years.**

Shadyab et al, 2016

Menopause is an Individual Experience

SYMPTOMS
DISEASES

Vulnerability depends on

- GENETIC DISPOSITION
- PERSONAL HISTORY
- LIFE-STYLE AND HEALTH CARE
- PSYCHO-RELATIONAL FACTORS
- SOCIO-CULTURAL ENVIRONMENT

↓

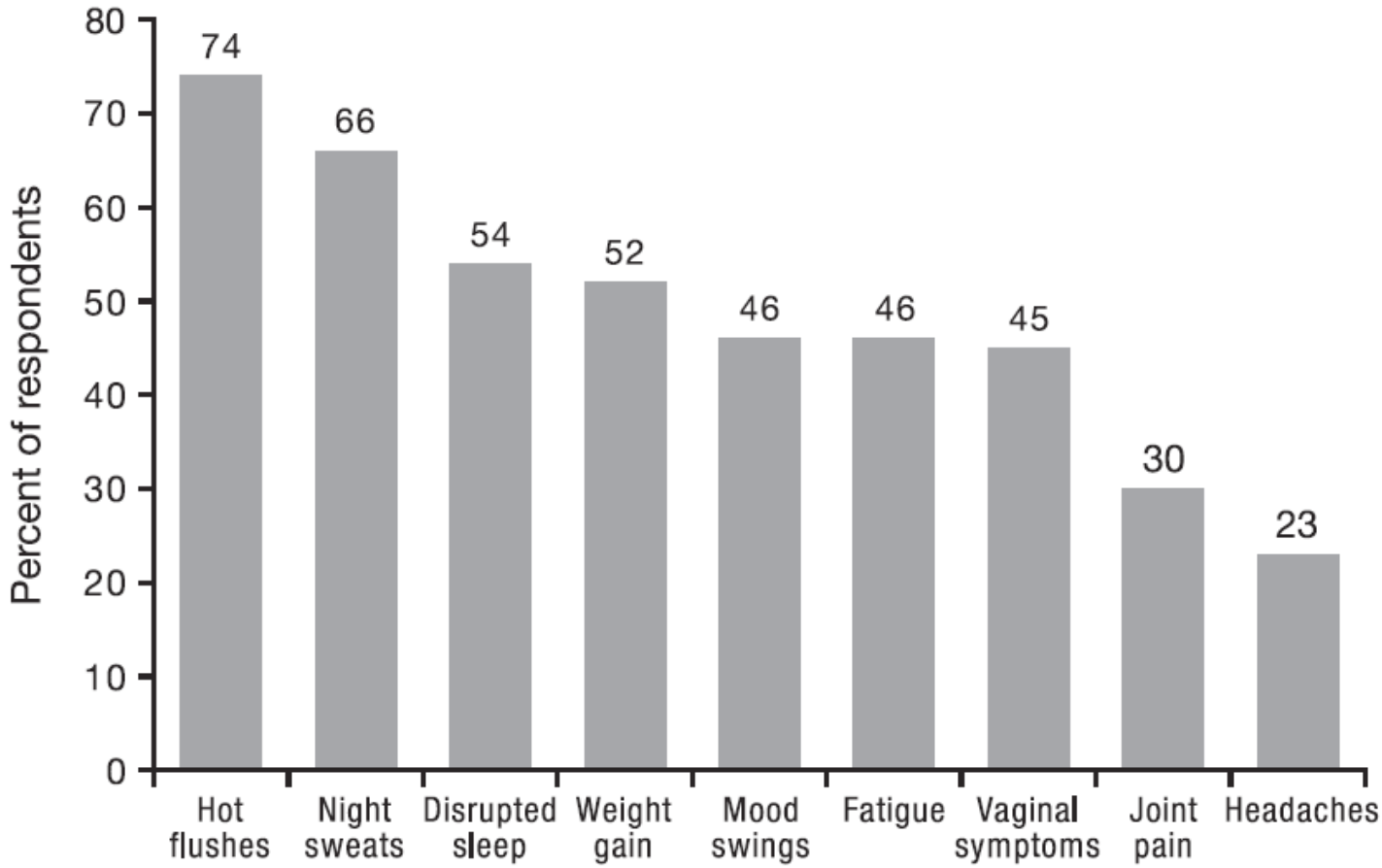
MULTI-SYSTEM IMPLICATIONS OF SEX HORMONES CHANGES

RE Nappi, 2013

Vaginal Health: Insights, Views & Attitudes (VIVA) – results from an international survey

R. E. Nappi and M. Kokot-Kierepa*

CLIMACTERIC 2012;15:36–44



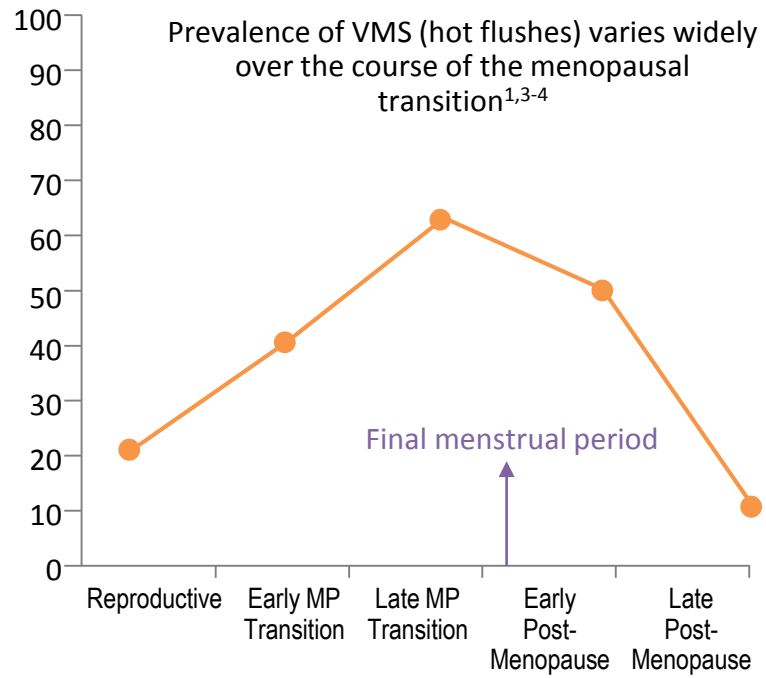
- **3520 postmenopausal women aged 55–65 years**

Frequency of VMS Varies Widely and Changes Over Time

Frequency of VMS varies widely from woman to woman

- The frequency of VMS has been shown to be significantly less in East Asian women compared with those from North America, Latin America, and Europe[1-3]
- Prevalence of hot flushes may be influenced by:[3]
  - Climate
  - Diet
  - Body mass
  - Reproductive patterns
  - Cultural attitudes towards menopause

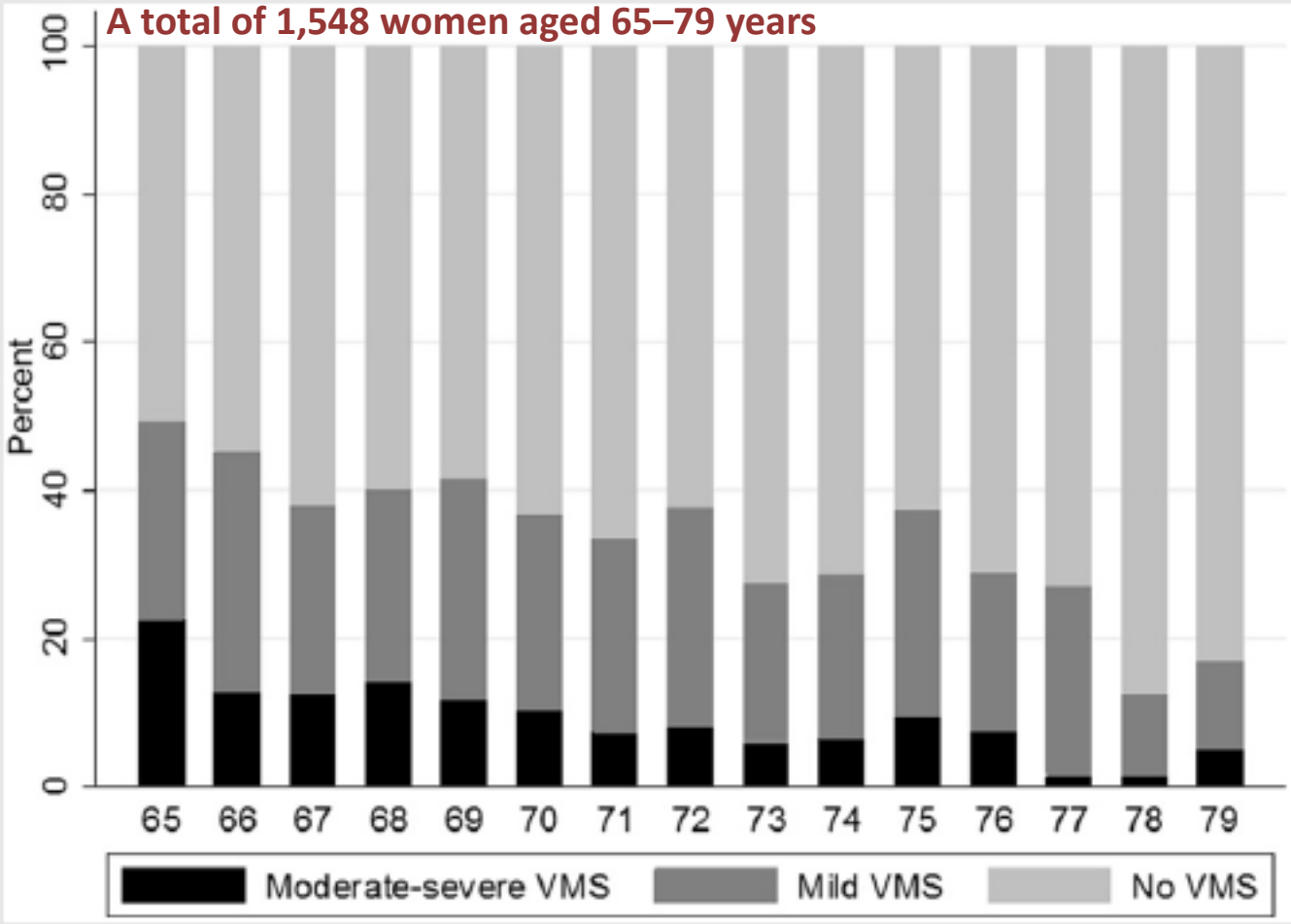
Frequency of VMS varies widely over time in an individual woman



Impact: Individualize management of menopausal women and follow them over time

1. Grady D, Barrett-Connor E. Menopause. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine,* 25th ed. 2016. Philadelphia, PA: Saunders Elsevier;2016: 1623-1629.
2. Lock M. *J Br Menopause Soc.*2002;8(4):132–136
3. Freeman EW and Sherif K. *Climacteric.* 2007;10:197–214.
4. Dennerstein L, et al. *Obstet Gynecol.* 2000;96:351-358.
5. DiBonaventura MD, et al. *Int J Womens Health*. 2013;5:261-269.

HOT-FLUSHES ARE COMMON ALSO IN OLDER WOMEN



Severity of vasomotor symptoms (VMS) by age of women.

- **Factors significantly associated with VMS were age, obesity, being a caregiver for another person, and bilateral oophorectomy.**

Zeleke et al, 2015

Vasomotor symptoms in menopause: a biomarker of cardiovascular disease risk and other chronic diseases?

- **Menopausal disorders may include shorter-term symptoms, such as hot flushes and night sweats (vasomotor symptoms, VMS) and longer-term chronic conditions such as cardiovascular disease (CVD), osteoporosis, and cognitive impairment.**

- **Initially, no clear link between the shorter-term symptoms and longer-term chronic conditions was evident and these disorders seemed to occur independently from each other. However, there is a growing body of evidence demonstrating that VMS may be a biomarker for chronic disease.**

Prevention of CVD in women, as for men, should be started early, and effective management of chronic disease in postmenopausal women has to start with the awareness that VMS during menopause are harbingers of things to come and should be treated accordingly.

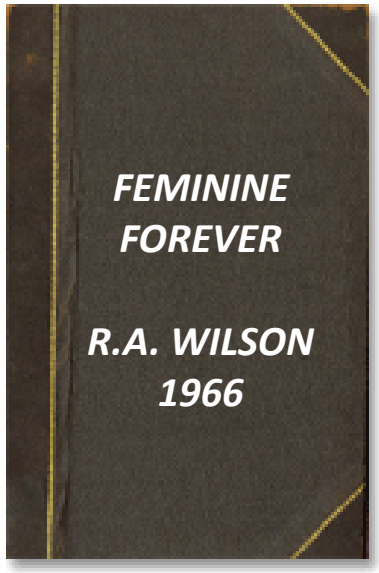
Biglia et al, 2017

Menopause – Natural Selection or Modern Disease?

Menopause is a natural phenomenon which may require treatment because:

- It may occur prematurely
- It is a turning point in the ageing process
- It may be associated with symptoms with a great impact on quality of life

From the Estrogen Elixir…

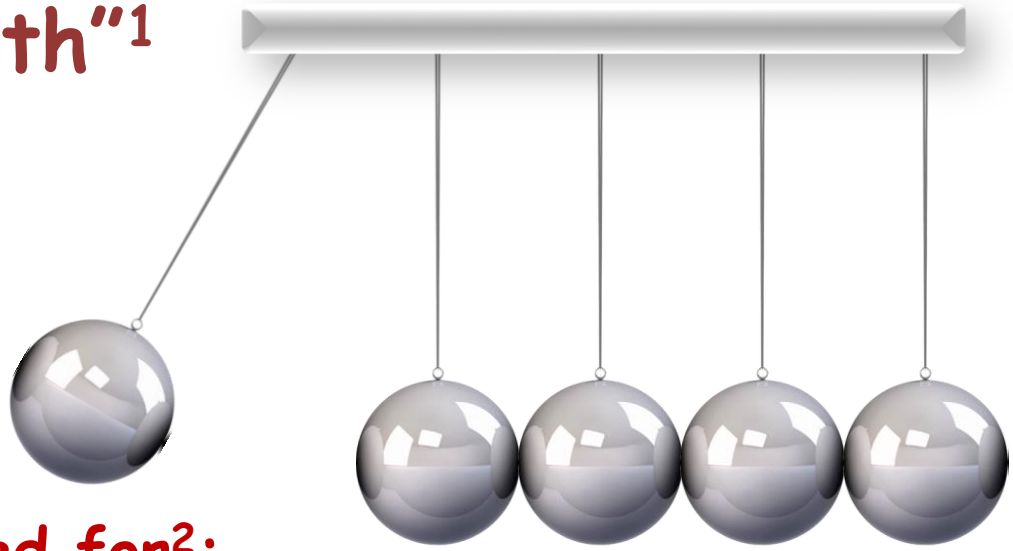


…to the Estrogen Poison!

RE Nappi, 2016

Fluctuating Views of Hormone Therapy (HT) Over the Years: The Golden Age

- HT long ago heralded as a female "fountain of youth"[1]



HT favored for[2]:

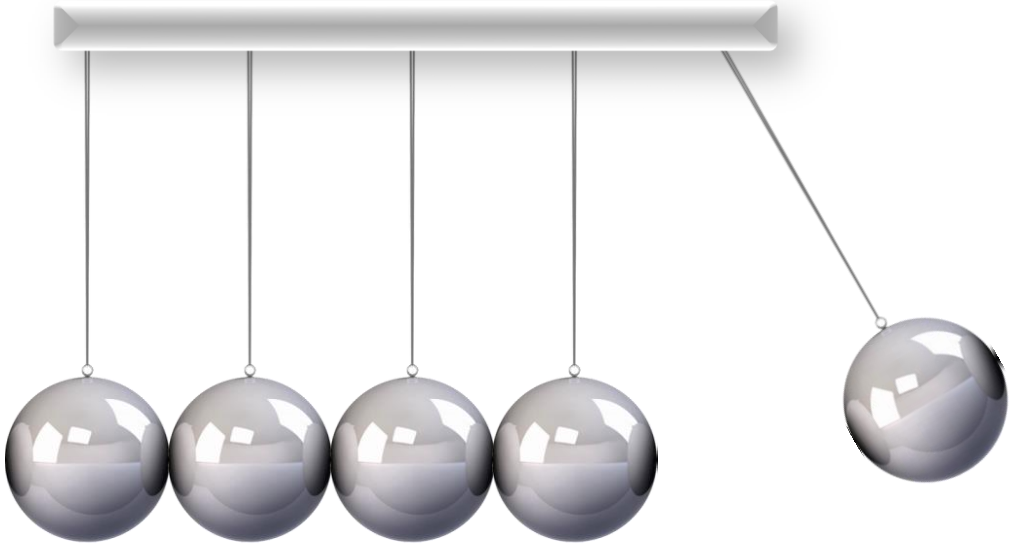
- Symptom relief
- Chronic disease prevention

1980-1990	1990-2000	2000-2010	2010-Present

1. Fisch J. http://acsh.org/2015/08/the-pendulum-swings-prescribing-hormone-replacement-therapy-13-years-after-the-womens-health-initiative-study/. August 2, 2015.
2. NICE. Menopause: Full Guideline, Version 1.5. nice.org.uk/guidance/ng23. November 12, 2015.

Fluctuating Views of HT Over the Years: Era of Fear and Concern

- HT falls from grace based on large, influential studies[1,2]



Key studies:

- Women's Health Initiative (WHI) (2002)[1]
- Million Women Study (2003)[2]

Risks described:[1,2]

- Breast cancer
- CHD
- Stroke
- VTE

1980-1990	1990-2000	2000-2010	2010-Present

1. Rossouw JE, et al. JAMA. 2002;288(3):321-333.
2. Beral V; Million Women Study Collaborators. Lancet. 2003;362(9382):419-427.

Risks and benefits of hormone therapy: has medical dogma now been overturned?

S. Shapiro, T. J. de Villiers, A. Pines†, D. W. Sturdee‡, R. J. Baber**, N. Panay††, J. C. Stevenson‡‡, A. O Mueck*** and H. G. Burger†††*

CLIMACTERIC 2014;17:215–222

Table 1 Women's Health Initiative: hazard ratios for intervention phase and cumulative follow-up of 13 years

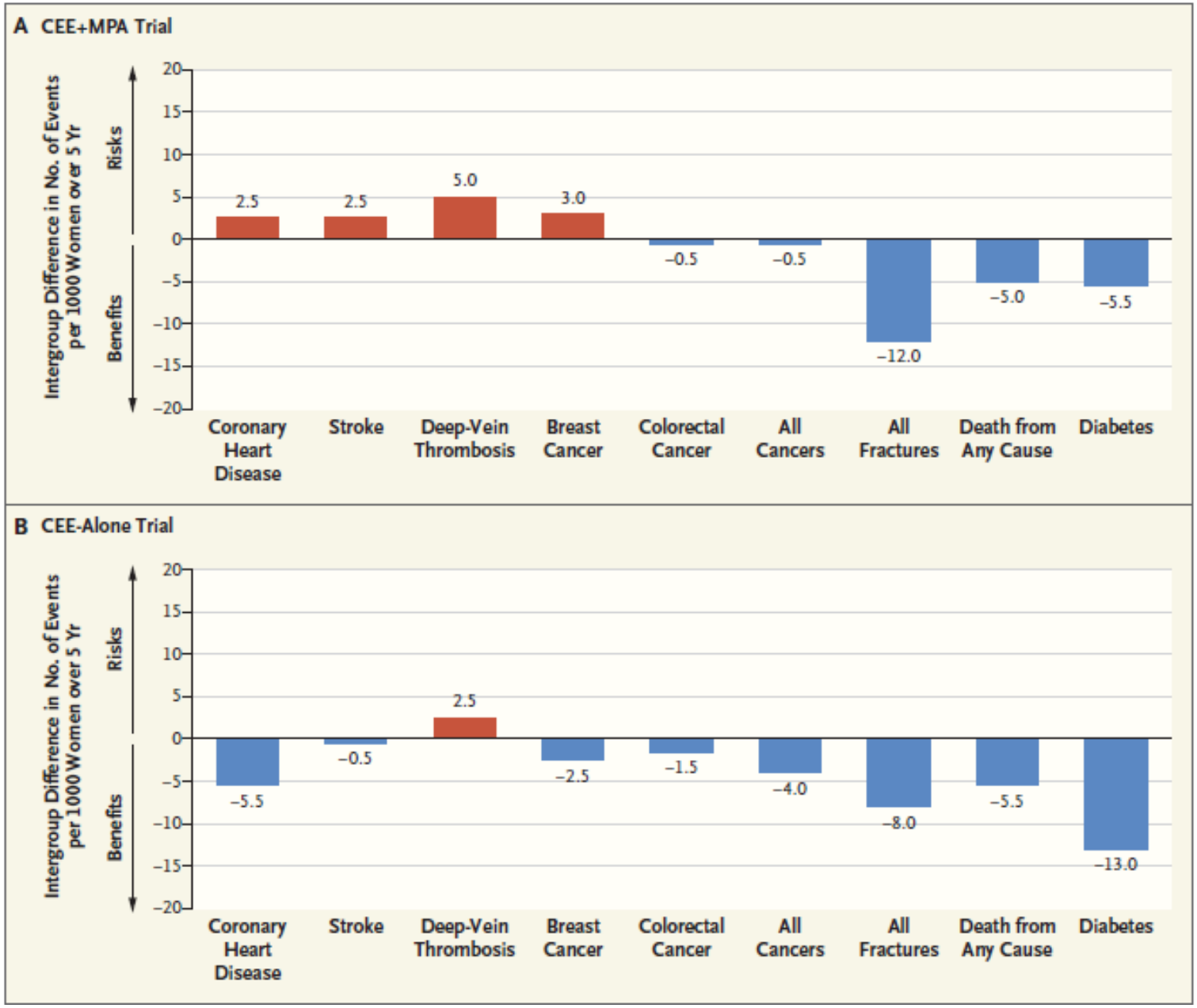
Outcome	*Exposed/controls*	*Hazard ratio*	*95% confidence interval*
E+P/placebo	8506/8102		
Intervention phase			
coronary heart disease	196/159	1.18	0.95–1.45
breast cancer	206/155	1.24	1.01–1.53
global index	876/736	1.12	1.02–1.24
Cumulative follow-up			
coronary heart disease	487/430	1.09	0.96–1.24
breast cancer	434/323	1.28	1.11–1.48
global index	2198/1997	1.06	1.00–1.13
ET/placebo	5310/5429		
Intervention phase			
coronary heart disease	204/222	0.94	0.78–1.14
breast cancer	104/135	0.79	0.61–1.08
global index	753/755	1.03	0.93–1.13
Cumulative follow-up			
coronary heart disease	363/393	0.94	0.82–1.09
breast cancer	168/216	0.79	0.65–0.97
global index	1374/1397	1.02	0.94–1.09

E+P, estrogen plus progestogen therapy; ET, estrogen therapy

CEE + MPA

For the EP and the ET recipients, all significantly elevated HR estimates were < 2 and even <1.5 for some. For such low estimates, particularly HRs of <1.5, it is impossible to discriminate among bias, confounding and causation as alternative explanations.

Benefits and Risks of the Two Hormone-Therapy Formulations Evaluated in the Women's Health Initiative



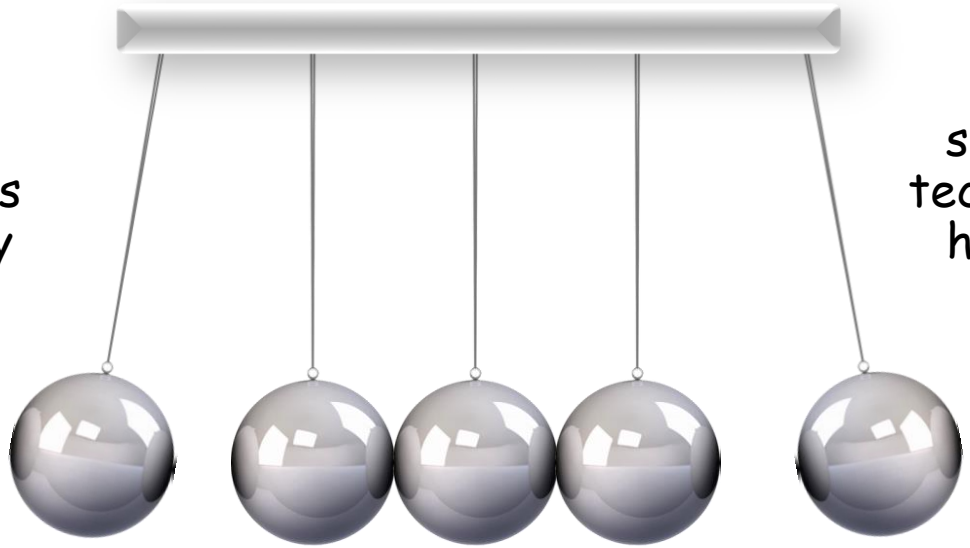
50-59 yrs

Manson & Kaunitz, 2016

Opportunity for Change Rests with a New Generation of Physicians

- Balancing Women's Needs with the Realities of HT

Some women still experience bothersome symptoms unnecessarily and may benefit from effective treatment



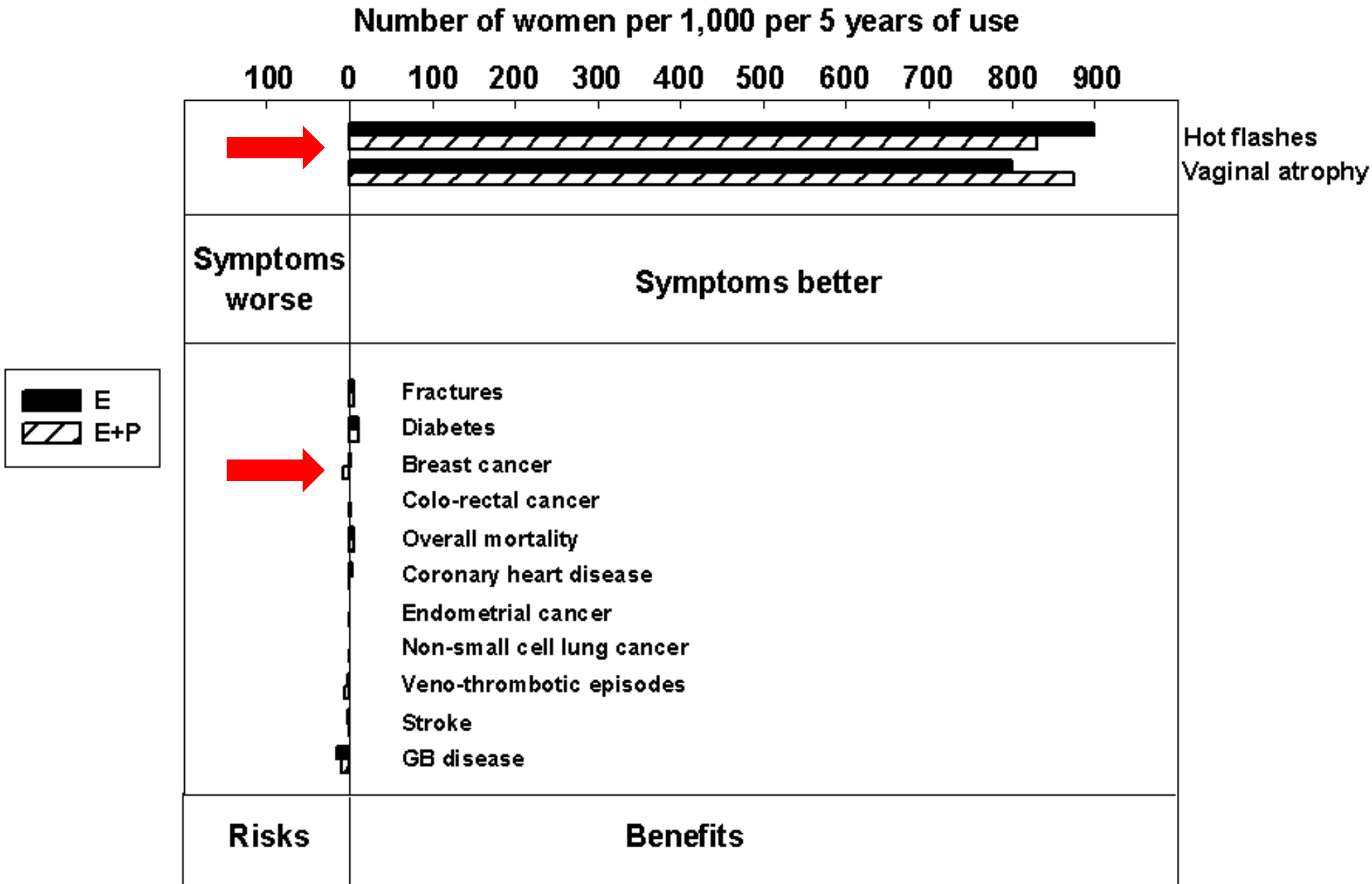
Some clinicians still need appropriate techniques and tools to help engage, educate, and effectively treat patients

Today, national and international societies support use of HT for women who desire it when benefits outweigh risks[1-6]

1980-1990	1990-2000	2000-2010	2010-Present

1. de Villiers, et al; International Menopause Society. Climacteric. 2013;16:316-337.
2. Guidozzi F, et al; South African Menopause Society. S Afr Med J. 2014;104:537-543.
3. North American Menopause Society. Menopause. 2012;19:257-271.
4. Mosconi P, et al; Italian Consensus Conference Working Group. BMC Womens Health. 2009;9:14.
5. NICE. Menopause: Full Guideline, Version 1.5. nice.org.uk/guidance/ng23. November 12, 2015.
6. Stuenkel CA, et al. *J Clin Endocrinol Metab*. 2015;100(11):3975-4011.

RISKS & BENEFITS INTO PERSPECTIVE



Santen et al, 2010

With Time Comes a Better Understanding of HT: 2010-Present

Age Matters[1]

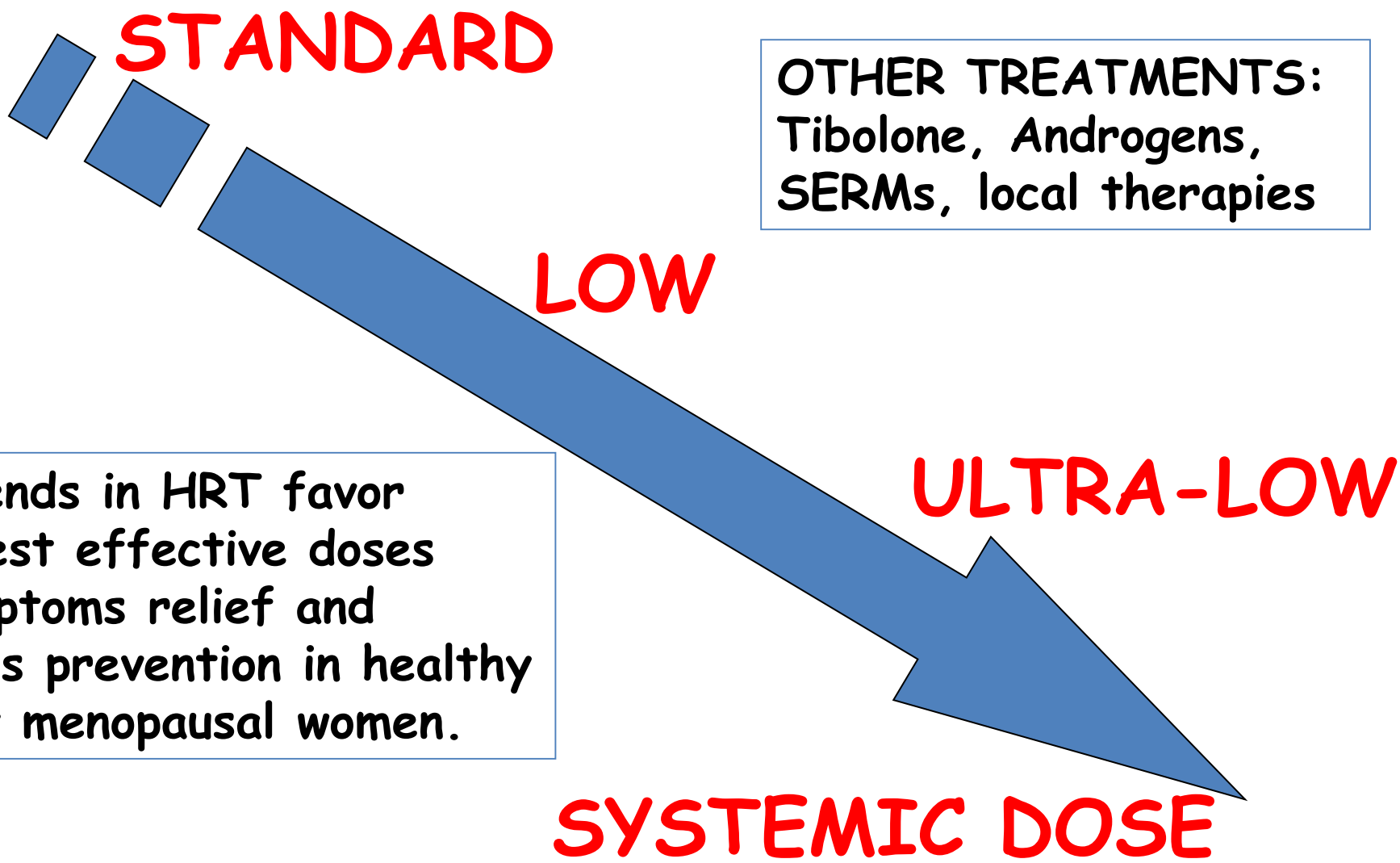
- In many instances, benefits of HT outweigh risks for women:
  - **50-59 year old *or***
  - **<10 years menopausal**
- Benefits in this population may include:
  - **Menopause symptom relief**
  - **Reduced mortality**
  - **Fracture prevention**
  - **Improved metabolic profile**
  - **Reductions in CHD**
  - **Reduced risk of some cancers**

The Type of HT Matters[1,2]

- Estrogen + progestogen appropriate for women with their uterus
- Unopposed estrogen appropriate for women without their uterus
- Local agents may be sufficient for vulvo-vaginal symptoms
- Systemic agents may be needed for vasomotor symptoms

1. Santen RJ, et al; Endocrine Society. *J Clin Endocrinol Metab*. 2010;95(7 Suppl 1):s1-s66.
2. de Villiers, et al; International Menopause Society. Climacteric. 2013;16:316-337.

HRT: AN EVOLVING CONCEPT FOR THE INDIVIDUALIZED CARE



OTHER TREATMENTS:
Tibolone, Androgens, SERMs, local therapies

New trends in HRT favor the lowest effective doses for symptoms relief and bone loss prevention in healthy recently menopausal women.

RE Nappi, 2008

Terapie ormonali della perimenopausa

EP contraccettivo	• Revisiona le controindicazioni a EP • Efficace su PMS/tensione mammaria/sanguinamento • Preferire basso dosaggio EE o E2
E2 orale/transdermico + LNG-IUD	Riduce/elimina il sanguinamento, ma non i sintomi ciclici
E2 sequenziale/continuo + progestinico ciclico	• Può verificarsi un sanguinamento irregolare • Possono persistere sintomi ciclici • Alcune donne lo preferiscono

modificato da Jane & Davis, 2014

E2 vs EE: different potency

Table 3 Relative potency of various estrogens concerning several clinical (relief of hot flushes) and metabolic parameters (suppression of follicle stimulating hormone (FSH) levels; increase in the serum levels of high density lipoprotein (HDL) cholesterol, sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG) and angiotensinogen). The values are estimated on a weight basis[12–14]

Estrogen	*Hot flushes*	*FSH*	*HDL cholesterol*	*SHBG*	*CBG*	*Angiotensinogen*
Estradiol-17β	100	100	100	100	100	100
Estriol	30	30	20			
Estrone sulfate		90	50	90	70	150
CEE	120	110	150	300	150	500
Equilin sulfate			600	750	600	750
Diethylstilbestrol		340		2 560	2 450	1 950
Ethinylestradiol	12 000	12 000	40 000	50 000	60 000	35 000

CEE, conjugated equine estrogens

50 mcg E2 is equivalent to 5 mcg EE

From Kuhl, 2005

CLINICALLY RELEVANT BIOCHEMICAL EFFECTS

Transdermal vs Oral

ET	Transdermal ET	Oral Relevance	Patient
HDL-C	↑	↑ ↑	CHD
LDL-C	↓	↓	CHD
Triglycerides	↓	↑ ↑	CHD
C-reactive protein	↔	↑	CHD
Renin substrate	↔	↑	Hypertension
Insulin resistance	↔	↑	Diabetes
CYP450 enzyme	↔	↑	Smokers
SHBG, TBG, CBG	↔	↑	Thyroid disease, persistent vasomotor symptoms
Estrone sulfate (SO_4)	↔	↑	Estrogen monitoring

CBG = corticosteroid-binding globulin; CHD = coronaryheart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TBG = thyroid-binding globulin; SHBG = sex-hormone–binding globulin.

Nachtigall LE. *Am J Obstet Gynecol*. 1995;173(3 pt 2):993–997 [Evidence Level C]; Campagnoli C. *Gynecol Endocrinol*. 1993;7:251–258 [Evidence Level B]; Godsland IF. *Fertil Steril.* 2001;75:898–915 [Evidence Level B]; Slater CC, et al. *Menopause*. 2001;8:200-203. [Evidence Level B]

Courtesy of S Berga, 2008

Biological activities of progestins

Progestins	Anti-estrogenic	Estrogenic	Androgenic	Anti-androgenic	Glucocorticoid	Anti-mineralocorticoid
Chlormadinone acetate	+	-	-	+	+	-
Cyproterone acetate	+	-	-	++	+	-
Dienogest	+/-	+/-	-	+	-	-
Drospirenone	+	-	-	+	-	+
Etonogestrel (3-keto-desogestrel)	+	-	+	-	-	-
Gestodene	+	-	+	-	+	+
Levonorgestrel	+	-	+	-	-	-
Medroxyprogesterone acetate	+	-	+/-	-	+	-
Nomegestrol acetate	+	-	-	+/-	-	-
Noresthisterone	+	+	+	-	-	-
Norgestimate	+	-	+	-	-	-
Progesterone	+	-	-	+/-	+	+

+ effective; - not effective; +/- weakly effective

Schindler AE *et al.* Maturitas 2008

Progestins are highly protective on the endometrium

Doses of oral progestogens for endometrial protection

These minimum doses are protective when given 12 days per calendar month.[35]

Norgestrel	0.15 mg
Noresthisterone	1 mg
Medroxyprogesterone acetate*	10 mg
Dydrogesterone	10 mg
Micronised progesterone	200 mg

*Equally protective as 2.5 mg daily continually throughout calendar month.

Nomegestrol acetate 5 mg

E Barrett- Connor, 1998

Revised Global Consensus Statement on Menopausal Hormone Therapy

- The following Consensus Statement is endorsed by The International Menopause Society, The North American Menopause Society, The Endocrine Society, The European Menopause and Andropause Society, The Asia Pacific Menopause Federation, The International Osteoporosis Foundation and The Federation of Latin American Menopause Societies.
- The revised statement contains only areas of consensus and does not replace the more detailed and fully referenced recommendations of the individual societies.

De Villiers et al, 2016

Global consensus statement on menopausal hormone therapy – an update

- The role and safety of tibolone, ospemifene and the tissue selective estrogen complex (TSEC) comprising conjugated estrogens and bazedoxifene. This recognizes the increasing complexity of therapeutic options;
- The role of alternative prescription therapies for menopausal symptoms;
- More detailed statements about fracture risk reduction;
- More detailed statements about the use of MHT in women with premature ovarian insufficiency or early menopause;
- Further information about the impact of MHT on mood changes at menopause;
- Broad statements on the overall management of midlife women's health.

Fenton & Panay, 2016

Revised Global Consensus Statement on Menopausal Hormone Therapy

- MHT, including tibolone and the combination of conjugated equine estrogens and bazedoxifene (CE/BZA), is the most effective treatment for vasomotor symptoms (VMS) associated with menopause at any age, but benefits are more likely to outweigh risks if initiated for symptomatic women before the age of 60 years or within 10 years after menopause.
- MHT, including tibolone and CE/BZA, is effective in the prevention of bone loss in postmenopausal women.
- MHT, including tibolone, can be initiated in postmenopausal women at risk of fracture or osteoporosis before the age of 60 years or within 10 years after menopause.
- The type and route of administration of MHT should be consistent with treatment goals, patient preference and safety issues and should be individualized. The dosage should be titrated to the lowest appropriate and most effective dose.

De Villiers et al, 2016

Revised Global Consensus Statement on Menopausal Hormone Therapy

- Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 years are at a higher risk for cardiovascular disease and osteoporosis and may be at increased risk of affective disorders and dementia. In such women, MHT reduces symptoms and preserves bone density.
- Observational studies that suggest MHT is associated with reduced risk of heart disease, longer lifespan, and reduced risk of dementia require confirmation in RCTs. MHT is advised at least until the average age of menopause.
- Estrogen as a single systemic agent is appropriate in women after hysterectomy but concomitant progestogen is required in the presence of a uterus for endometrial protection with the exception that CE can be combined with BZA for uterine protection.

De Villiers et al, 2016

Revised Global Consensus Statement on Menopausal Hormone Therapy

- MHT, including tibolone, is effective in the treatment of vulvovaginal atrophy (VVA), now also considered as a component of the genitourinary syndrome of menopause (GSM).
- Local low-dose estrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or associated discomfort with intercourse or for the prevention of recurrent urinary tract infections.
- Ospemifene, an oral selective estrogen receptor modulator, is also licensed in some countries for the treatment of dyspareunia attributed to VVA.

❖ Please, NOTE vaginal DHEA is coming to treat VVA/GSM!!!

De Villiers et al, 2016

Revised Global Consensus Statement on Menopausal Hormone Therapy

- The option of MHT is an individual decision in terms of quality of life and health priorities as well as personal risk factors such as age, time since menopause and the risk of VTE, stroke, ischemic heart disease and breast cancer. MHT should not be recommended without a clear indication for its use.
- Duration of treatment should be consistent with the treatment goals of the individual, and the benefit/risk profile needs to be individually reassessed annually. This is important in view of new data indicating longer duration of VMS in some women.
- MHT includes a wide range of hormonal products and routes of administration, including tibolone (where available) or CE/BZA, with potentially different risks and benefits. However, evidence regarding differences in risks and benefits between different products is limited.

De Villiers et al, 2016

2016 IMS Recommendations on Women's Midlife Health and Menopause Hormone Therapy

- An absolute increase in weight at midlife is not attributable to the menopause [B].
- The hormonal changes that accompany menopause are associated with increases in total body fat and abdominal fat, even in lean women [B].
- Maintenance of a healthy diet, avoidance of caloric excess and physical activity are important components of weight management [A].
- Menopausal abdominal fat accumulation is ameliorated by estrogen therapy, with a reduction in overall fat mass, improved insulin sensitivity and a lower rate of development of type 2 diabetes [A].
- Obesity, personal history of thrombosis (superficial or deep) and genetic thrombophilia are common VTE risk factors. Transdermal estrogen therapy should be the first choice in obese women suffering from climacteric symptoms [B].

Baber at al, 2016

Terapie ormonali della postmenopausa

Utero intatto

- Terapia combinata (EP) transdermica
- E2 orale/transdermico (cerotto, gel) + Progesterone orale o vaginale/Progestinico orale/LNG-IUD
- Tibolone
- TSEC (CE/BZA)

Post-isterectomia

- E2 orale/transdermico
- Tibolone
- TSEC (CE/BZA)

modificato da Jane & Davis, 2014

A Practitioner's Toolkit for Managing the Menopause

F. M. Jane and S. R. Davis

MHT dosing[1]

Estrogen

	Low dose	Moderate dose	High dose
CEE	0.3–0.45 mg/day	0.625 mg/day	1.25 mg/day
17β-estradiol	0.5 –1.0 mg/day	1.5–2 mg/day	2 mg
Estradiol valerate	0.5 mg/day	1 mg/day	2 mg/day
Transdermal estradiol patch	25–37.5 µg/day	50 µg/day	75–100 µg/day
Estradiol hemihydrate gel	0.5 mg/day	1.0 mg/day	1.5 mg/day

Sequential P – daily dose for 14 days per month- lowest "safe" dose with:

	Low dose E	Moderate to high dose E
Dydrogesterone	5 mg	10 mg
Micronized progesterone	100 mg	200 mg
MPA	5 mg	5–10 mg
Norethisterone acetate (NETA)	1.25 mg	1.25–2.5 mg

Continuous P – daily dose – lowest "safe" dose with:

	Low dose E	Moderate to high dose E
Dydrogesterone	5 mg	5–10 mg
Drospirenone	0.5 mg	—
Micronized progesterone	100 mg	100 mg
MPA	2.5 mg	2.5–5 mg
Norethisterone acetate (NETA)	0.5–1.0 mg	>1.0–2.5 mg
LNG-IUD	device releasing 20 µg/24 hours	

Tibolone

Tibolone	2.5 mg daily

CLIMACTERIC 2014;17:1–16

BREAST CANCER & ROLE OF PROGESTINS

Table 3 Effect of various types of hormone replacement therapy on the relative risk of invasive breast cancer, compared with never use (modified from Fournier *et al.*[91])

Hormone replacement therapy	*Number of breast cancers*	*Relative risk (95% confidence interval)*
Estrogen orally/percutaneously	76	1.29 (1.02–1.65)
Estrogen + progesterone	129	1.00 (0.83–1.22)
Estrogen + dydrogesterone	108	1.16 (0.94–1.43)
Estrogen + other progestins	527	1.69 (1.50–1.91)

from EPIC, 2008

What binds to estrogen receptor (ER)

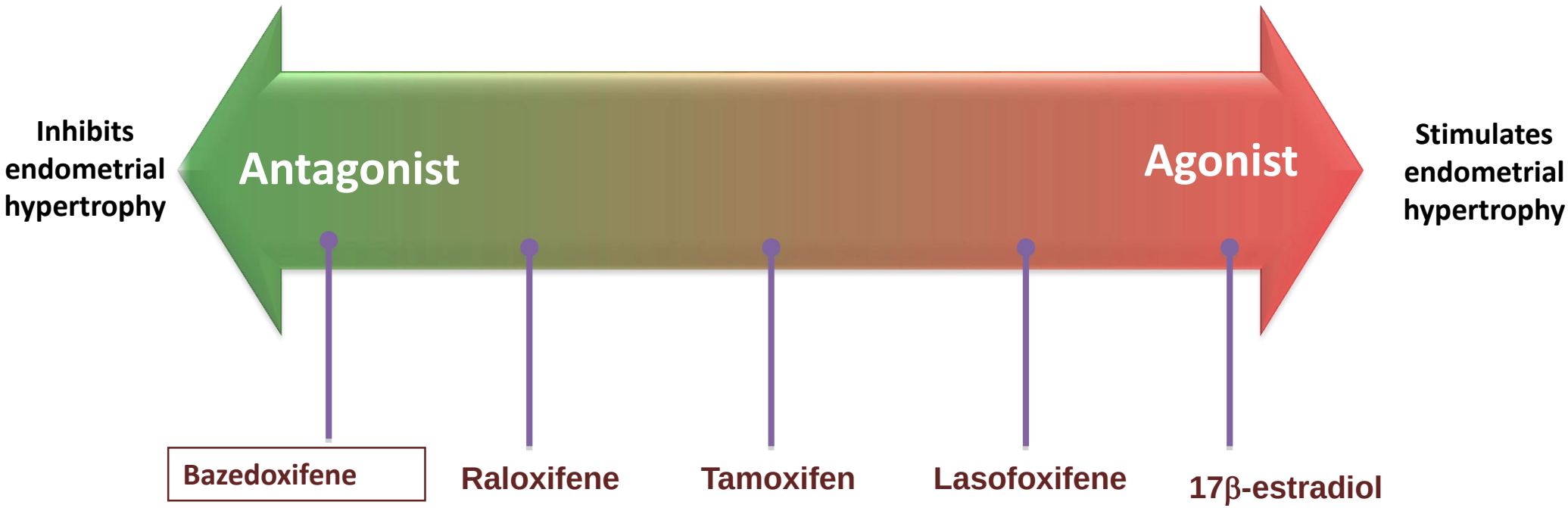
- Natural estrogens are produced by the ovary
  - E_2 is the most potent estrogen known and the primary estrogen in premenopausal women[1,2]
  - Estrone is the predominant estrogen in postmenopausal women[1]
- CEE is a natural formulation of an extract prepared from pregnant mares' urine that contains
  - Ten classical estrogens, estrone and 17 –estradiol
  - A group of unique ring B unsaturated estrogens such as equilin and equilenin
- SERMs
  - Molecules that are not reproductive hormones structurally but share a part of the structure
  - Has estrogen-like effects in some tissues. Blocks estrogen effects in some tissues

1. Barnes BB, Levrant SG. Pharmacology of Estrogens. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects.* 3rd ed. San Diego, CA: Academic Press; 2007:767-777. **2.** Dey M. *Maturitas.* 2000;34:S25-S33. **3.** *ACOG. Pract Bull.* 2014;114:1-15. 3.Riggs BL, Hartmann LC. Selective estrogen-receptor modulators – mechanisms of action and application to clinical practice. N Engl J Med 2003;348:618–29
4.Bhavnani BR, Stanczyk FZ J Steroid Bio & Mol Biol (2014) 142, 16-19

Courtesy of J Calaf Alsina, 2016

Estrogens and SERMs: Different Effect on Endometrium*

Why Bazedoxifene instead of other SERMs?



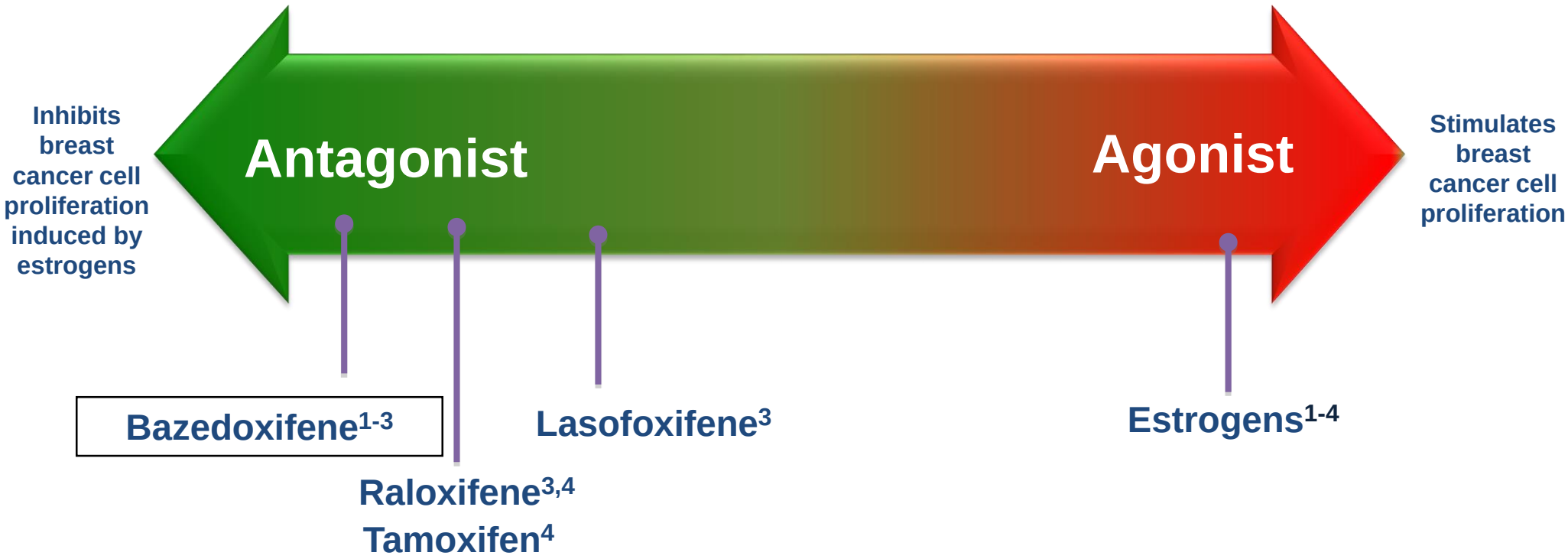
SERM: Selective Estrogen Receptor Modulator

* In vivo studies

Courtesy of J Calaf Alsina, 2016

Why Bazedoxifene instead of other SERMs?

In Vitro Studies
Cell Proliferation In Breast Cancer Cells



SERM: Selective Estrogen Receptor Modulator

1. Komm BS, et al. *Ann N Y Acad Sci*. 2001; 2. Komm BS, et al. *Endocrinology*. 2005;

3. Chang KCN, et al. *J Steroid Biochem Mol Biol.* 2010; 4. Nuttall ME, et al. *Am J Physiol Cell Physiol*. 2000;

Courtesy of J Calaf Alsina, 2016

A Practitioner's Toolkit for Managing the Menopause

F. M. Jane and S. R. Davis

Evidence-based non-hormonal treatment [1] for vasomotor symptoms

Estrogen and SERM therapy

CEE 0.45 mg plus bazedoxifene	20 mg daily

SSRI or SSRI/SNRI– low dose (also treats menopausal mood disorder)	Venlafaxine 75mg, desvenlafaxine 50mg, escitalopram 10 mg, paroxetine 7.5 mg daily
Clonidine	100 µg daily
Gabapentin	300 – 900 mg daily
Pregabalin	75 – 150 mg twice a day
Hypnosis	
Cognitive behavior therapy	
Weight loss for obese women	
Stellate ganglion blockade*	Severe resistant VMS

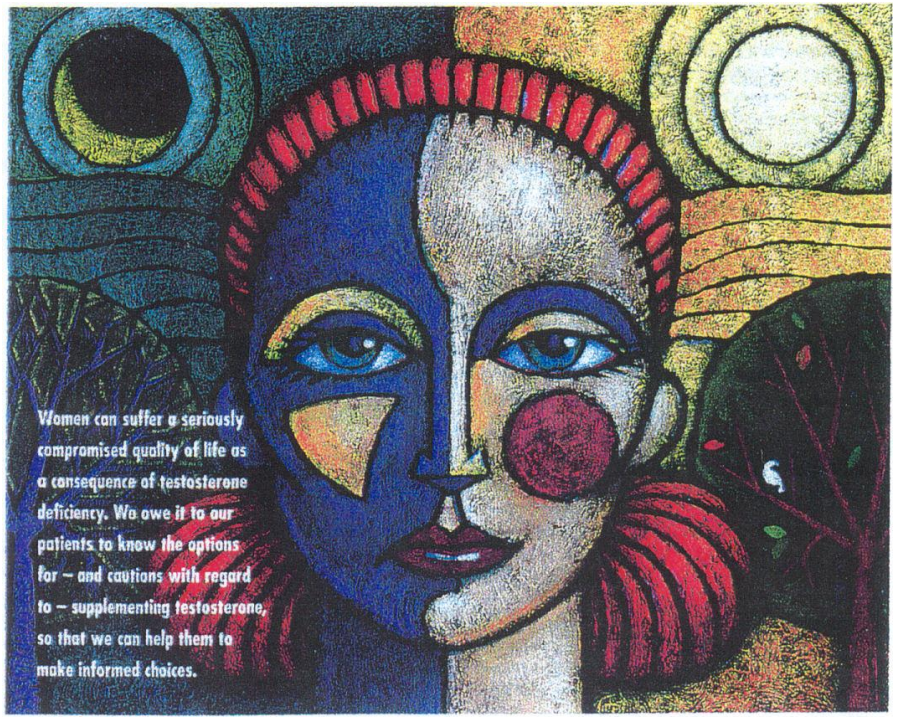
*specialist referral

[1] – Availability of hormonal/nonhormonal treatment and indications for use from regulatory bodies vary between countries.

CLIMACTERIC 2014;17:1–16

ANDROGEN THERAPY IN WOMEN HAS A LONG HISTORY!

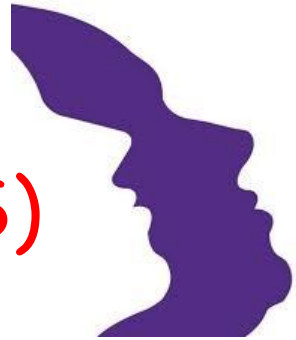
- Used well before the pharmaceutical industry was interested (Greenblatt RB. Androgenic therapy in women. *Endocrinology* 2:665-6. 1942)
- 1st randomized, double-blind, placebo controlled trial reported in 1950 (Greenblatt et al. Evaluation of estrogen, androgen, and estrogen-androgen combination and a placebo in the treatment of menopause. *JCEM* 10:1547-58, 1950)



ERT/ART relieved hot flushes, improved well-being and libido and produced a "smoother transition"

RE Nappi, 2008

ANDROGEN THERAPY IN WOMEN (IMS)



Key points

- Androgen levels decline with age in women with no significant change associated with the natural menopause [A]
- There is strong evidence that androgens influence female sexual function and that testosterone therapy may be useful for women with arousal or desire disorders [A]
- Women should be fully assessed for other treatable causes of sexual dysfunction before testosterone therapy can be considered
- Testosterone therapy should be considered as a clinical trial which should not be continued if a woman has not experienced benefit by 6 months [A]

Baber at al, 2016

ANDROGEN THERAPY & OTHER TARGETS: RISKS AND BENEFITS BALANCE STILL UNDER INVESTIGATION

Key points

- Observational studies indicate that testosterone has favourable cardiovascular effects measured by surrogate outcomes; however, associations between endogenous testosterone and the risk of cardiovascular disease and total mortality, particularly in older women, are yet to be established. Adverse

Davis & Wahlin-Jacobsen, 2016

TREATMENT WITH ANDROGENS

- The Revised Global Consensus on MHT supports the use of continuous testosterone therapy, either alone or with MHT, in carefully selected postmenopausal women with sexual interest/arousal disorder (in countries with regulatory approval).

De Villiers et al, 2016

- NICE guidelines (2015) indicate to consider testosterone supplementation for menopausal women with low sexual desire if HRT alone is not effective.

- According to the 2016 IMS Recommendations, Tibolone, a synthetic steroid classified as a selective tissue estrogenic activity regulator, is of value in treating postmenopausal women with FSD «1+», whereas systemic DHEA therapy is not effective over that of placebo in terms of improved sexual function, well-being or metabolic health in postmenopausal women.

Baber et al, 2016

Tibolone in postmenopausal women: a review based on recent randomised controlled clinical trials

NICOLETTA BIGLIA[1], SILVIA MAFFEI[2], STEFANO LELLO[3], & ROSSELLA E. NAPPI[4,5]

- **S**elective
- **T**issue
- **E**strogenic
- **A**ctivity
- **R**egulator

- Estrogenic, progestogenic, androgenic properties
- SERM profile achieving biological effects without directly modulating the estrogen, androgen, or progesterone receptors
- Various metabolites exert their effects directly on these receptors or by modulating endogenous steroid activity within different tissues

Abstract

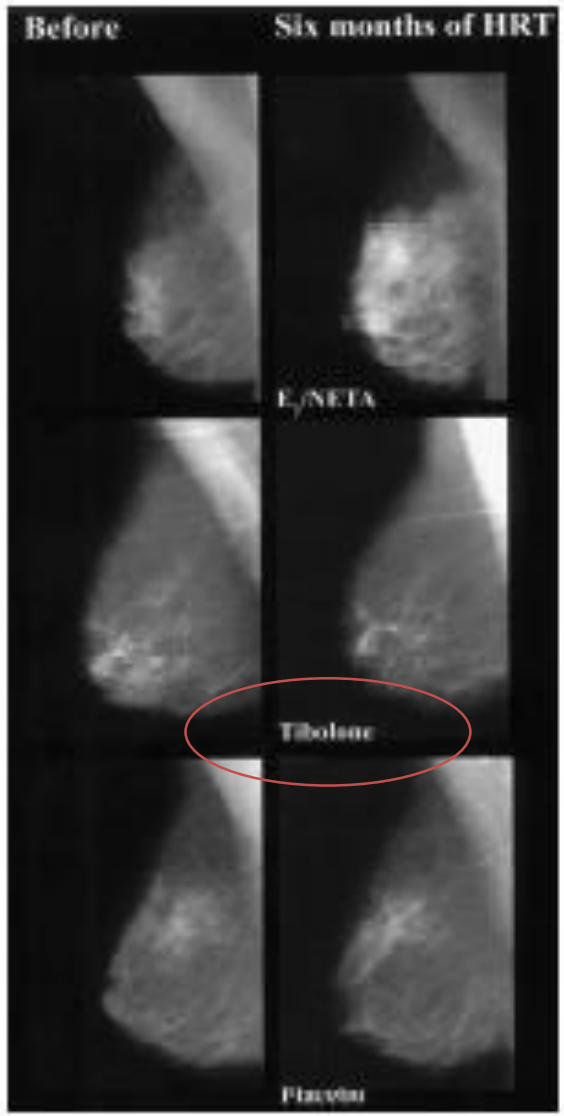
Aim. To critically discuss the use of tibolone (T), in light of a series of very recent double-blind placebo (PL) controlled trials (LISA, LIFT, OPAL, THEBES, LIBERATE) conducted worldwide in a large number of postmenopausal women (PMW).

Methods. The most relevant publications on T therapy in PMW were considered with emphasis on menopausal symptoms, quality of life, sexuality, bone, cardiovascular system (CVS) and oncologic risk.

Results. T significantly relieves climacteric symptoms and improves mood and sexual well-being (LISA). T is as effective as estrogen–progestin therapy in preventing bone loss and reducing the relative risk of vertebral and non-vertebral fractures (LIFT). By using surrogate endpoints of the individual risks for the CVS, studies show mixed results, but a favourable effect on acute miocardial infarction and thromboembolism has been documented (THEBES, LIFT, OPAL). Although findings about endometrial and colon cancer are reassuring, conclusive data on breast cancer risk with T are not available and an increased risk of recurrence in women with previous breast cancer emerged (LIBERATE).

Conclusions. T is effective in treating menopausal syndrome with a good tolerability profile. In spite of some unsolved issues in term of safety, T is still a good treatment option for early PMW.

Gynecol Endocrinol, 2010



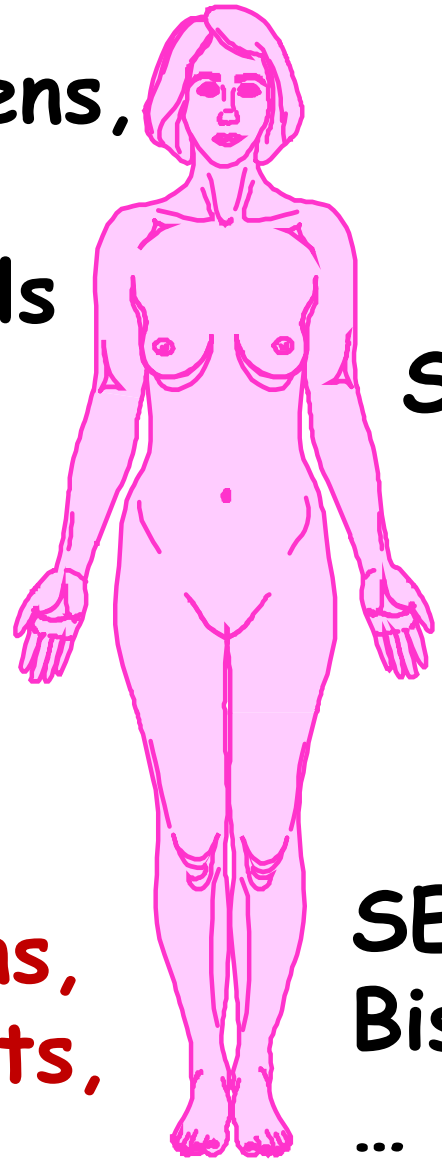
Lundstrom et al, 2002

‘PROFOX’ – the post HRT nightmare

J. Studd

Phytoestrogens,
Other
nutraceuticals

Psychoactive
Agents



Statins

HRT

Local
Estrogens,
Lubricants,
…

SERMs
Bisphosphonates,
…

CLIMACTERIC 2010; Early Online, 1–3

Use of Plant-Based Therapies and Menopausal Symptoms
A Systematic Review and Meta-analysis

RESULTS In total, 62 studies were identified, including 6653 individual women. Use of phytoestrogens was associated with a decrease in the number of daily hot flashes (pooled mean difference of changes, −1.31 [95% CI, −2.02 to −0.61]) and vaginal dryness score (pooled mean difference of changes, −0.31 [95% CI, −0.52 to −0.10]) between the treatment groups but not in the number of night sweats (pooled mean difference of changes, −2.14 [95% CI, −5.57 to 1.29]). Individual phytoestrogen interventions such as dietary and supplemental soy isoflavones were associated with improvement in daily hot flashes (pooled mean difference of changes, −0.79 [−1.35 to −0.23]) and vaginal dryness score (pooled mean difference of changes, −0.26 [−0.48 to −0.04]). Several herbal remedies, but not Chinese medicinal herbs, were associated with an overall decrease in the frequency of vasomotor symptoms. There was substantial heterogeneity in quality across the available studies, and 46 (74%) of the included randomized clinical trials demonstrated a high risk of bias within 3 or more areas of study quality.

CONCLUSIONS AND RELEVANCE This meta-analysis of clinical trials suggests that composite and specific phytoestrogen supplementations were associated with modest reductions in the frequency of hot flashes and vaginal dryness but no significant reduction in night sweats. However, because of general suboptimal quality and the heterogeneous nature of the current evidence, further rigorous studies are needed to determine the association of plant-based and natural therapies with menopausal health.

Franco et al, 2016

Managing the menopause: An update

Table 5
Additional educational resources of therapies for menopausal symptoms.

Patient information
1. Pamphlet: Menopause. Should I take HRT? http://bestpractice.bmj.com/best-practice/pdf/patient-summaries/en-gb/532536.pdf 2. Cochrane Consumer network http://consumers.cochrane.org/healthcare-users-cochrane 3. National Center for Complementary and Alternative Medicine, US National Institutes of Health

Intervention	Conclusion	Reference
Acupuncture	No evidence of significant difference for flushes when acupuncture was compared with sham acupuncture.	S. Dodin, C. Blanchet, I. Marc, E. Ernst, T. Wu, C. Vaillancourt, et al., Acupuncture for menopausal hot flushes. Cochrane Database Syst. Rev. (2013) Issue 7. Art. No: CD007410. Doi: 10.1002/14651858. CD007410.pub2.)
Yoga	Does not improve VMS	K.M. Newton, S.D. Reed, K.A. Guthrie, K.J. Sherman, C. Booth-LaForce, B. Caan, et al., Efficacy of yoga for vasomotor symptoms: a randomized controlled trial, Menopause (2014) 21, 339–346. Doi: 10.1097/GME.0b013e31829e4baa
Phytoestrogens	No flush benefit overall with the exception of products containing a minimum of genistein 30 mg per day	H. Roberts, A. Lethaby, Phytoestrogens for menopausal symptoms: a Cochrane review summary, Maturitas (2014) 78, 79–81
Omega 3	Does not improve VMS	L.S. Cohen, H. Joffe, K.A. Guthrie, K.E. Ensrud, M. Freeman, J.S. Carpenter, et al., Efficacy of omega-3 for vasomotor symptoms treatment: a randomized controlled trial, Menopause (2014) 21, 347–354. Doi: 10.1097/GME.0b013e31829e40b8.
Exercise for flushes	Exercise is not an effective treatment for vasomotor menopausal symptoms.	A.J. Daley, A. Thomas, A.K. Roalfe, H. Stokes-Lampard, S. Coleman, M. Rees, et al., The effectiveness of exercise as treatment for vasomotor menopausal symptoms: randomised controlled trial, BJOG (2015) 122, 565–575. B. Sternfeld, K.A. Guthrie, K.E. Ensrud, A.Z. LaCroix, J.C. Larson, A.L. Dunn, et al., Efficacy of exercise for menopausal symptoms: a randomized controlled trial, Menopause (2014) 21,330–338

Roberts & Hickey, 2016

Menopausal Women and HCPs – A Therapeutic Alliance

- Understanding women's views on menopausal symptoms and consequences
- Helping women recognize and understand menopausal symptoms
- Counselling on the most important risk factors after menopause
- Selecting MHT and/or other treatments as appropriate and facilitating an informed decision by counselling women on the benefits and risks, taking into consideration their attitudes, preference and any safety issue. Annual reassessment is indicated.

RE Nappi, 2016

Aiming at "Precision Therapy" in Menopausal Women

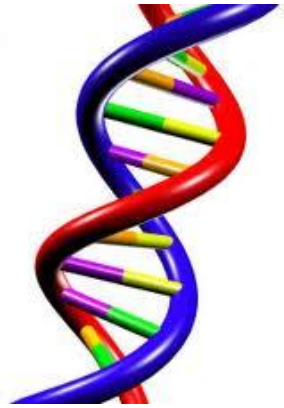
- Consider Guidelines on Menopausal Therapy and on other Conditions in the context of Menopausal Medicine.
- Promote Primary Prevention and a healthy Diet and Life-Style.
- Control Blood Pressure and other CVD Risk Factors.
- Supplement with Vitamin D, when needed.

- Type, Route, Dose, Duration of MHT should be tailored on the individual woman taking into account goals, efficacy, compliance, tolerability and any other relevant aspect.

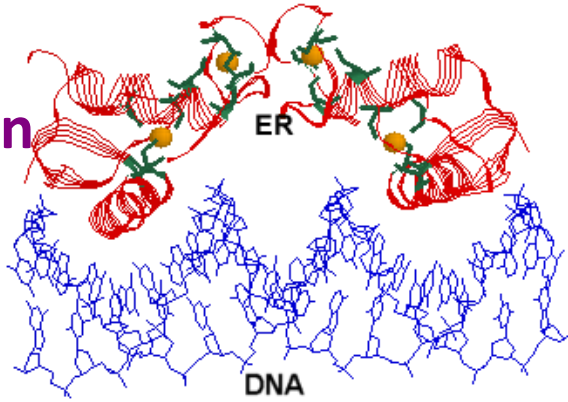
RE Nappi, 2016

Individualizing HT with Pharmacogenetics/Pharmacogenomics – Vanity or Vanguard?

- **The endocrinology of the menopausal transition is complex.**



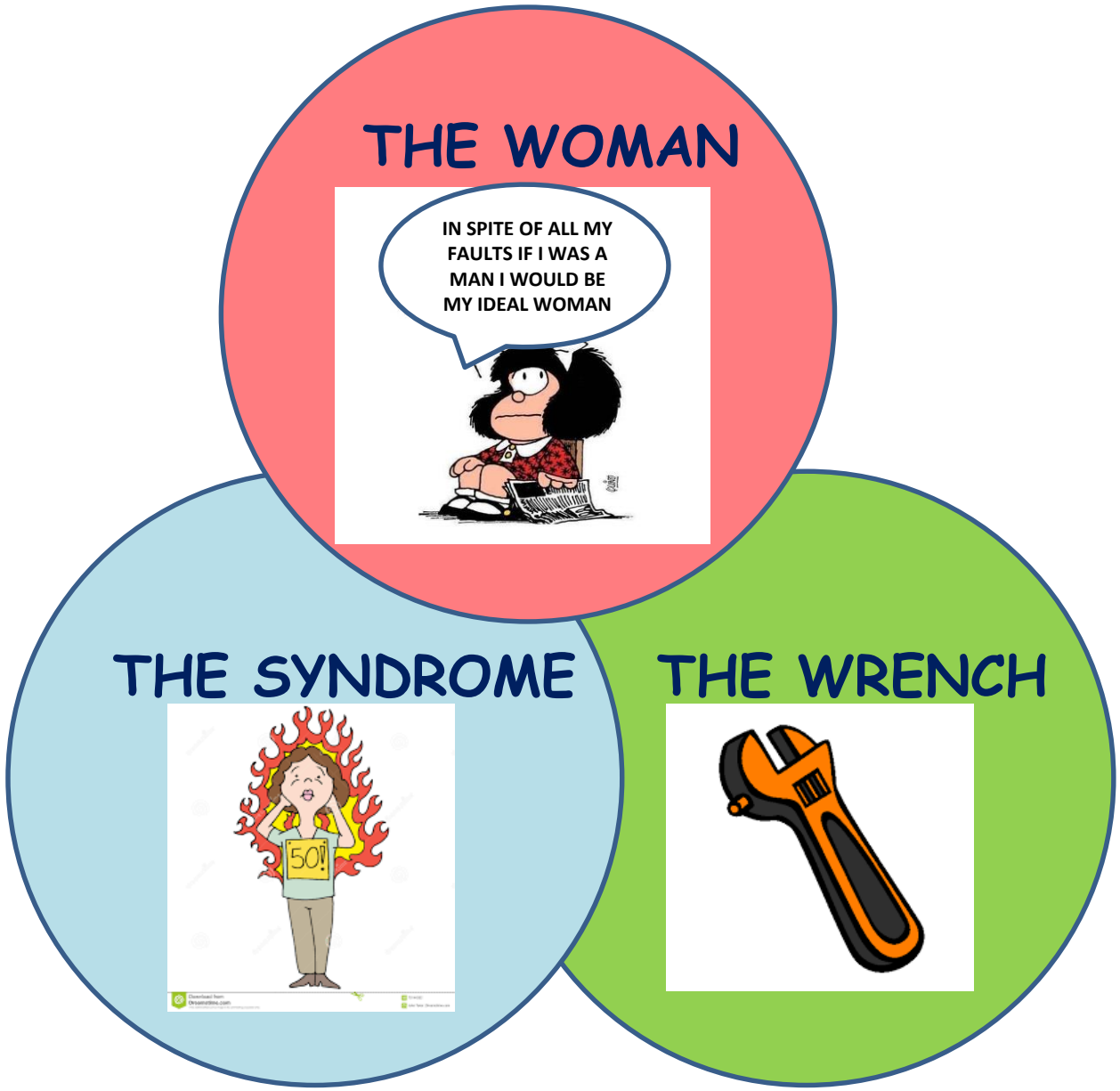
- **Advances in molecular and genomic science have confirmed that every woman is unique and has a *thumbprint* that will determine her response to physiologic events and to lifetime risks of disease.**



- **Variations in the genetically determined biology of women will determine the symptomatic response of a given menopausal woman to her physiologic decrease in estrogen synthesis *(and eventually in progesterone and androgens)* and postmenopausal metabolism to her response (or non response) to MHT.**

M Notelovitz, 2007

MHT – The Decision Making Process



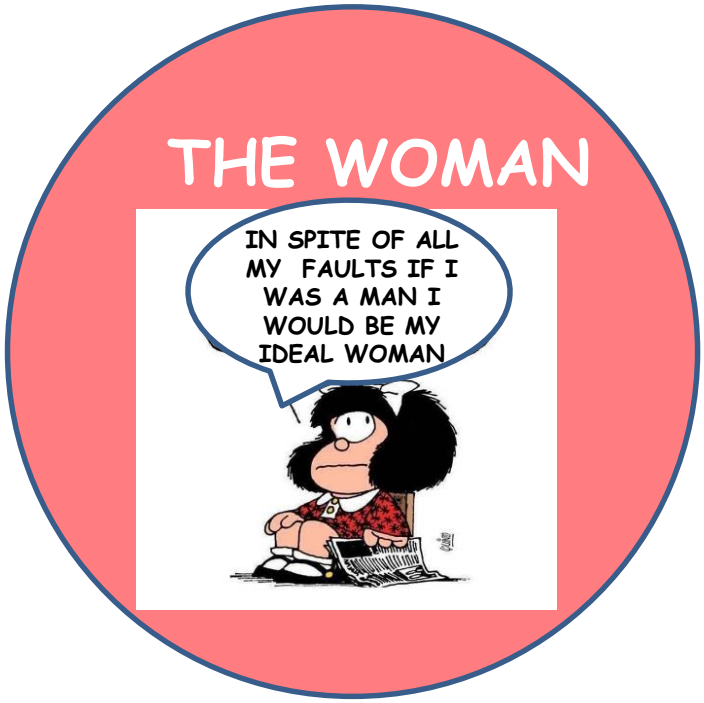
RE Nappi, 2016

Where Clinical Phenotypes at Menopause Come From (1)

GENERAL

- Age
- Education
- Family History
- Personal History
- Chronic Conditions
- Malignancies
- Medications
- Previous VTE
- Diet
- Exercise
- Smoking
- Caffeine
- Alcohol
- Recreational Drugs
- Partner
- Work
- Life-Style
- Stress
- Sexual Habits

- *Other Psycho-Relational and Environmental Factors*



REPRODUCTIVE

- Age at Menarche/Pregnancy/Menopause
- Menstrual Cycle History
- Contraceptive History
- Secondary Amenorrhea
- Anorexia Nervosa
- Polycystic Ovarian Syndrome
- Endometriosis
- Infertility
- Recurrent Miscarriages
- PMS/PMDD/PPD
- Menstrual Migraine/Other hormone-related headaches
- Parity
- Gestational Hypertension
- Gestational Diabetes
- Type of Menopause
- Hereditary Genital/Breast Cancers
- Pelvic Floor Dysfunction
- Previous Use of Hormones and Side-Effects

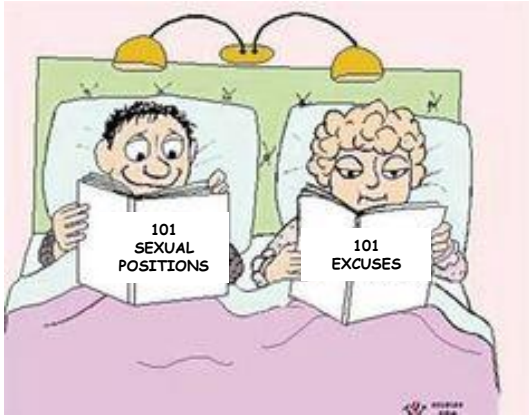
RE Nappi, 2016

Where Clinical Phenotypes at Menopause Come From (2)

THE SYNDROME

MENOPAUSAL SYMPTOMS

- Type
- Frequency
- Severity
- Onset
- Duration



RE Nappi, 2016

Where Clinical Phenotypes at Menopause Come From (3)

VITAL SIGNS AND CLINICAL INVESTIGATIONS

- Body Weight
- Waist/Hip Ratio
- Blood Pressure

- Glucose
- Lipids
- Vitamin D

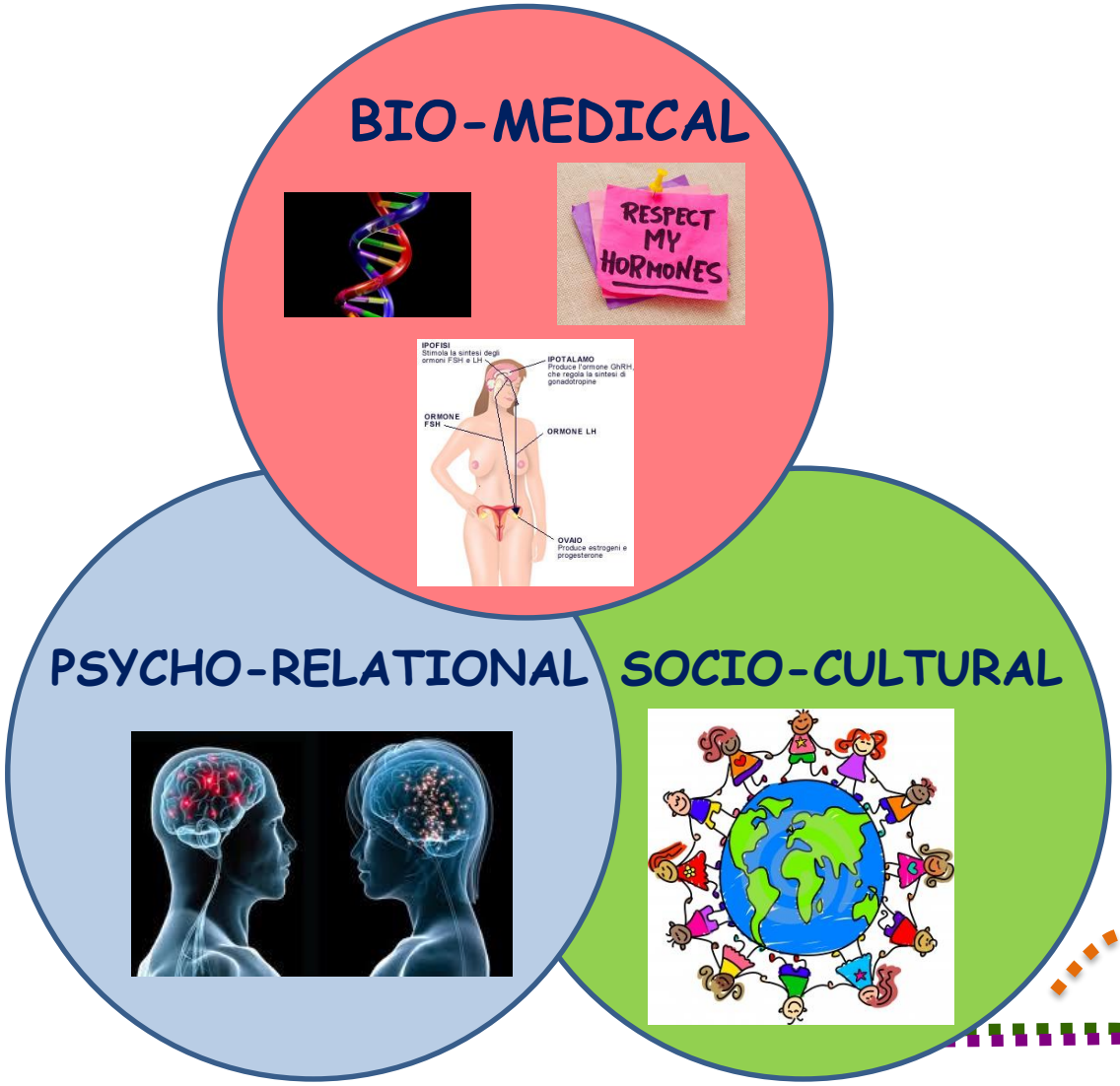
- Breast Density
- Endometrial Thickness
- Other Gyn Ultrasound Parameters

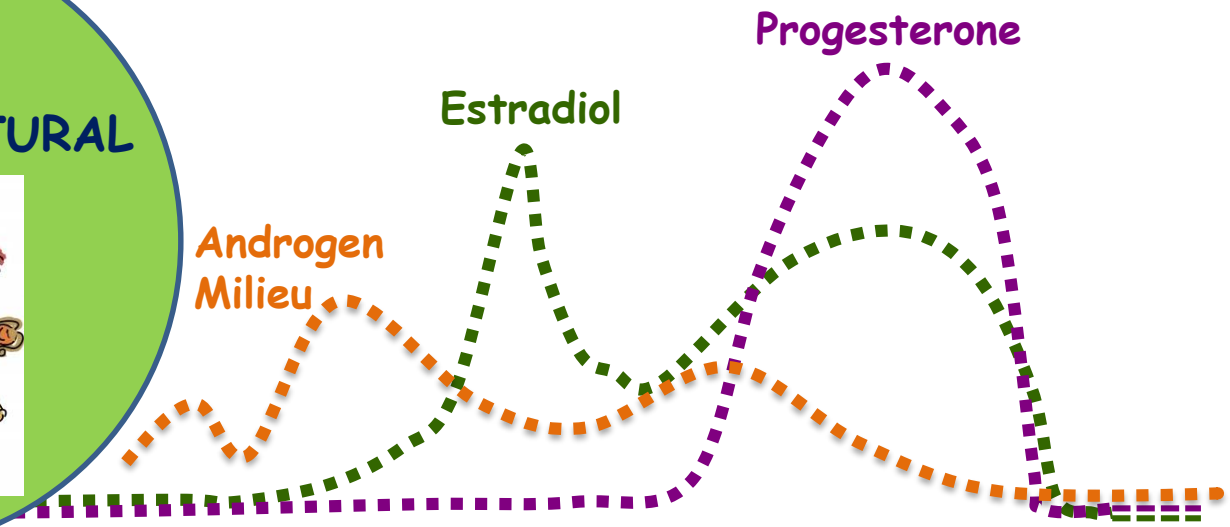
- Bone Mineral Density

- Other individual Bio-Medical Investigations

RE Nappi, 2016

Menopause is a Unique Experience in Women's Life





RE Nappi, 2016

GRAZIE DELL'ATTENZIONE

Endocrinologia Ginecologica e della Menopausa - IRCCS «Policlinico S. Matteo»

Unità di Clinica Ostetrica, Ginecologica e della Riproduzione Umana,
Dipartimento di Scienze Cliniche, Chirurgiche, Diagnostiche e Pediatriche,
Università degli Studi di Pavia

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