MENOPAUSAL HORMONAL THERAPY

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Framework

To assess HT role in controlling menopause-associated symptoms that may affect QoL & sex.

Does “MENOPAUSE” need to be treated?
IS MENOPAUSE MODERN?

MEAN AGE AT MENOPAUSE

Hawaiians 49.20
South African whites 51.44
South African Bantu 50.70
Netherlands 51.4
United States 49.0

Pavelka and Fenigan 1991
IS MENOPAUSE A PATHOLOGICAL CONDITION?

PREMENOPAUSAL

Fatigue
Cramping
Irritability
Bloating
Infertility

If the symptoms don't subside after the period, visit a doc!

POSTMENOPAUSAL

HEADACHES AND HOT FLASHES
BODY AND PUBIC HAIR BECOMES THICKER AND DARKER
SKIN AND MUCOUS MEMBRANES BECOME DRIER, SKIN DEVELOPS A ROUGHER TEXTURE
STRESS OR URG RE INCONTINENCE
VAGINAL DRYNESS, ITCHING AND SHRINKING
HAIR BECOMES THINNER AND LOSES LUSTER
BONES LOSE MASS AND BECOME MORE FRAGILE
RISK OF CARDIOVASCULAR DISEASE
BACKPACES
NIPPLES BECOME SMALLER AND FLATTEN
ABDOMEN LOSES SOME MUSCLE TONE

QoL

TREATMENT WITH HORMONES

OC
FSH-LH
E2 P4
HORMONAL DEFICIENCIES + SYMPTOMS

Androgen deficiency

Androgen, progesterone, and estrogen deficiency

Abrupt

Steadily

25  35  45  55  65  75  85

ANDROGENS  ESTROGENS
MENO-PAUSE
IS NOT SEX-PAUSE

Bertolino ISSM Newsbulletin 2009  Menopause is not sex-o-pause,  Bertolino MV et al  La salud sexual luego del la menopausia libro de Medicina Sexual  2011

SEXUALITY IS A VITAL FUNCTION THROUGHOUT LIFE
a. ARE "THEY" STILL HAVING SEX?

Women in red

Which percentage of women over 60 do you think is still sexually active?

N=63

gyn: 20-40%

Bertolino Congreso Gerontología 2013

a. ARE “THEY” STILL HAVING SEX?

Lindau et al 2000 N=1455
Aerobic activity in bouts of 10 min (GR Ia)

Moderate intensity: 150 min/week

Vigorous intensity: 75 min/week

Federal Physical Activity Guidelines 2008

LIFESTYLE

≈ 60% TV

<5% exercise

Dysmobility syndrome
Osteoporosis + Sarcopenia
Disability & falls.

What’s in a name revisited: should osteoporosis and sarcopenia be considered components of “dysmobility syndrome?”

Binkley, D. Krueger, B. Buehring

DOI 10.1007/s00198-013-2427-1
TREATMENT: QoL & Sexual health

WHICH?

HOT FLASHES

GUMS

SEXUAL DYSFUNCTION

MOOD & BRAIN

MUSCULOSKELETAL EFFECTS
WHO?

Too young for menopause?

IIIG*  SURGICAL  POST THERAPIES

* immunologic; infectious, idiopathic, genetic
WHAT?

ESTROGEN

TESTOSTERONE

PROGESTERONE

TIBOLONE

SERMS

DHEA
Estrogen

ORAL vs TRANSDERMAL

“The lower dose, for the shortest period of time.”

- CEE 0.3 - 0.625 - 1.25 mg/d
- E2 valerate 1 – 2 mg/d
- E2 micr 0.5-1 – 2 mg/d

PATCH

E2 ALONE:
14, 25 , 50, 100 mcg/d/7 d

COMBINED :
25/50 mcg E2+ 25mg/250 NETA/ 24 h

NOMA 2.50 mg + E2 (hemi-hidrate) 1.55 mg
LNG 0.25 mg. + E2 valerate 2 mg

Vasomotor symptoms
Osteoporosis –related fractures in at high-risk women

GEL
17 b E2 1,25g gel/ pulse .
Dose: 1-2/day.

0.06%: Low dose 0.75 mcg /d
WHICH route?

<table>
<thead>
<tr>
<th>ESTROGENS</th>
<th>Oral</th>
<th>Transdermal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st pass effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Renin</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>TG</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>LDL c and HDL</td>
<td>↓/↑</td>
<td>↓/-</td>
</tr>
<tr>
<td>Cost</td>
<td>less</td>
<td>more</td>
</tr>
<tr>
<td>VTE risk (OR)</td>
<td>4.2</td>
<td>0.9</td>
</tr>
</tbody>
</table>

2013
**Tablets:**
- E3 0.5 mg
- Promestriene: 0.01 g

**Cream:**
- E3 1 gr. 1 mg
- Promestriene: 100 gr of cream; 1 gr de promestriene

**Vaginal ring**
releases estradiol, 7.5 mcg per 24 hours,
in a consistent stable manner over 90 days.

**Genitourinary menopausal symptoms**
Progestins

Natural

Synthetic

Progestins

P4

Pregnanes

Acetylated

yes

no

MPA

CYP

CMA

MGA

Dydro-

gesterone

NOMA

Pro-

Tri-

De-

tegestone

yes

no

17-Net

LINESTRENOL

1

Noretinodrel1

Estranes

Gonanes

norgestrel

DSG

LNG

GDN

NGM

DNG# 4

Espiron.*

DRP

Natural

20 mcg/day

17-α

CH2CN

*DERIVATIIVES

# antiandrogen

yes

to

Endometrium

brain

bones & muscles

Synthetic
SAFETY ISSUES of ESTROGEN AND PROGESTINS

WHI warning

2002: TH prescription dropped 80%

Based on Rossouw et al 2007 data
CHD and MHT: The window

< 10 yrs post menopause or < 60 yrs age

Young    Old

Mendelsohn and Karas 2005; Salpeter et al 2006, Lisabeth and Bushnell 2012; images sphweb.bumc.bu.edu
STROKE and MHT: Dose Route Duration

**Age**

- 50-59
- 60-69
- 70-79

**Years since menopause**

- <10
- 10 to 19
- >20

**Cases per 100 Person-Years**

- MHT
- PBO

**LOW**
- <50 mcg/d
- 0.81

**HIGH**
- <0.625mg/d
- <2mg/d
- 1.89
- 1.25
- 1.48

*Adjusted RR vs never user

**For >1 year**

1.35 (1.20 to 1.52)

Renoux et al BMJ 2010

Bath and Gray BMJ 2006
VTE and MHT: type of steroid

Adjusted ORs (95% CI) for VTE users vs. non-users

- Oral estrogen: OR 11.6 (95% CI 4.2, 30.6)
- Transdermal estrogen: OR 2.1 (95% CI 0.9, 4.7)
- Micronized progesterone: OR 1.9 (95% CI 0.7, 5.2)
- Pregnane derivatives: OR 2.3 (95% CI 0.9, 5.7)
- Norpregnane derivatives: OR 1.5 (95% CI 0.4, 5.7)

Source: Canonico M. Circulation 2007
BREAST CANCER and MHT: progestin

-May I get breast cancer with TH?

RR: 1.26 (95%CI 1.00–1.59) (CEE + MPA)
Rossouw JE et al. 2002

International Menopause Society Statement on Breast Cancer

- Better risk profile: E2 + Micronized progesterone
- Risk is small: < 1 /1000 women / year of use.
  – less than associated with lifestyle: poor physical activity, obesity and alcohol
## Testosterone

<table>
<thead>
<tr>
<th>Route</th>
<th>Formulation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>MetilTo 2.50 mg/d</td>
<td></td>
</tr>
<tr>
<td>Sublingual</td>
<td>Intranasal</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>Propionateate To 2mg</td>
<td></td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Nandrolone 25–50 mg/ 4 sem</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>Patch 300 mcg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cream To 1% and Gel</td>
<td></td>
</tr>
</tbody>
</table>

**Improved:** Sexual desire, satisfaction, orgasm and coital frequency.

**Good safety and tolerability profile**

**Risks dose and duration–dependent**

- Nachtingall et al JSM 2007
- FDA 2004 [www.fda.gov/](http://www.fda.gov/)
Recommend

- against diagnosing testo deficiency in women.
- against prescribing To to otherwise healthy women.
- avoid prescribing To to improve sexual dysfunction *.

Suggests

-prescribing To: woman diagnosed *HSDD (personal distress).
-3-6 month trial of To to see if therapy improves sexual function.

Long-term risks: breast or cardiovascular are unknown.

BLISS (To Gel)  Snabes M. White et al 2012: 3,656 women /5,800 women-years of exposure )

31 CV events (lower than anticipated) event rate of 0.53%.

19 breast cancers, a rate of 0.33%
little data to support the use of DHEA or TIBOLONE in healthy postmenopausal women to improve reduced sexual function and well-being  
Pluchino et al 2013 and JCEM 2014

TIBOLONE approved for Climacteric symptoms.
MHT bottom lines: **BENEFITS**/risks

- Lessen hot flashes, night sweats, poor sleep, irritability, “brain fog”.
- Improve vaginal symptoms, painful intercourse.
- Ease OAB and recurring UTI with local Estrogens.

Do not prescribe for the prevention of chronic conditions

- Lower risk of CHD if started within 10 years of menopause
- Helps prevent bone fractures later in life, women at risk.
- Lower risk of developing type 2 diabetes.

Based on NAMS, USPSTF, ACOG, AHA, 2012-2013
Breast CA
- ET: 7 (10) years before the breast cancer risk increases.
- EPT: risk goes up after 3-5 years of use.
- EP (micronized P4), intermittently, early start: might ▼ risk

Endometrial CA
- Progesterone to prevent Endometrial CA.

VTE:
- risk increases with oral vs transdermal estrogen
- risk is higher with MPA vs micronized P4

- Both ET and EPT increases stroke risk. Low dose transdermal E2
- Do not use for dementia and depression
- Increased risk of gallbladder disease RR 1.7
• many patients **unnecessarily being denied** MHT.

• **healthy lifestyle** as part of the integral treatment.

• **tailor treatment** (dose, duration & scheme).
  - minimal dose to control symptoms shortest period of time.
  - right to be informed and decide.

• **E2P4**: vasomotor and GUM symptoms. **Testosterone** : HSDD

• Opportunities: Low evidence : encourage protocols.
We don’t stop laughing because we grow old,

We grow old because we stop laughing.

THANKS FOR YOUR ATTENTION