Hormone replacement therapy for pre-menopausal women with breast and gynecological cancer: impact on mood and sexual desire.

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IMPACT OF DISEASES ON SEXUAL WELL-BEING

- PRIMARY Diagnosis (acute/chronic)
- SECONDARY (side-effects, surgery, drugs...)
- TERTIARY (self-image, self-esteem, depression, social and relationship issue...)

PERSONAL HISTORY (education, experiences, partner...)

RE Nappi, 2005
BREAST CANCER IN YOUNG WOMEN

Table 1: Incidence of breast cancer by age

<table>
<thead>
<tr>
<th>Age</th>
<th>Annual incidence/100,000 women</th>
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<tbody>
<tr>
<td>&lt;20</td>
<td>0.1</td>
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<tr>
<td>20–24</td>
<td>1.4</td>
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<td>25–29</td>
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<td>35–39</td>
<td>58.4</td>
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<tr>
<td>40–44</td>
<td>116.1</td>
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<tr>
<td>45–49</td>
<td>198.5</td>
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</table>


- 2.7% of BC between 25–35 yrs (Axelrod et al, 2008)
KEY SEXUAL ORGANS IN WOMEN: 3) THE BREASTS

**Sensitivity**

**Arousal**

**Orgasm**

**Symbols**
- Womanliness
- Livelihood

**Targets**
- Sex Hormones
- Erotic Stimulation

**Effectors**
- Become engorged & pink/red
- Erection of nipples due to the stimulation of sensitive nerve endings

**Physical RESPONSES**

**SEXUAL FUNCTION**

RE Nappi, 2003
KEY SEXUAL ORGANS IN WOMEN: 2) THE GENITALS

Vulva
- Sensitive to touch & pressure
- Rich of small vessels & sensory nerve endings

Clitoris
- Erectile organ highly vascularized & innervated
- Comprises glans, body & crura & consists of 2 paired corpora cavernosa with vestibular bulbs surrounding the urethra
- Is devoted to pleasure

Vagina
- Interface of the coitus
- Produces neurogenic transudate to guarantee lubrication
- In the anterior fornix is located the controversial G-spot (glandular & vascular tissues)

Uterus
- Changes position during coitus
- Contracts during orgasm

Perception & Reaction of Pleasure

Sensorial Impulses

Arousal
Engorgement
Lubrication

Physical RESPONSES

SEXUAL FUNCTION

RE Nappi, 2003
NERVE SPARING SURGICAL TECHNIQUES FOR GYNECOLOGICAL MALIGNANCIES

- Autonomous pelvic nerves are essential for bladder and rectum function as well as sexuality.
- These nerves are usually permanently damaged during radical oncological surgery and this results in urological, sexual and proctological morbidity.
- Japanese surgeons have paved the way for surgical approaches to dissect these nerves during surgery and leave them intact.
- Significant progress has been made in understanding the neuroanatomy and the neurophysiology of autonomic pelvic plexus.
- There is not yet a consensus concerning to which part of uterine support ligaments a NS approach should be directed.

Trimbos et al, 2003; Raspaglesi et al, 2007
The female inferior hypogastric (= pelvic) plexus: anatomical and radiological description of the plexus and its afferences—applications to pelvic surgery

- Useful landmarks for a safe surgical approach during pelvic surgery;
- The new concept of NSRH has to be considered in order to reduce morbidity without compromising the oncological disease control.

Mauroy et al, 2007
**PREMATURE MENOPAUSE**

- Spontaneous ovarian failure affects, on average, 1% of women younger than **40 years**
- Iatrogenic menopause for benign and malignant conditions affects **3.4-4.5%**
- Abrupt sex-steroid withdrawal in surgical menopause vs variable lag time between medical treatments and onset of premature menopause
- Approximately 25% of breast cancer patients are **premenopausal** at diagnosis
- In premenopausal women chemotherapy combined with endocrine treatments causes premature menopause in over **80%** of patients during the 1° year after diagnosis.

*Anasti, 1998; Goodwin et al, 1999; Luborsky et al, 2003*
IATROGENIC PREMATURE MENOPAUSE IN MALIGNANCIES

- Type of Cancer
- Stage
- Prognosis
- Age at Diagnosis
- Surgical Approach
- Conservative vs Radical Treatment
- Adjuvant Chemotherapy and/or Radiotherapy
- Associated Side-Effects
- Severity of Recurrence

Ganz et al, 1996; Graziottin & Basson, 2004
SEX HORMONES & SEXUAL FUNCTION

PREMATURE MENOPAUSE

MENTAL AROUSAL

DESIRE

ORGASM SATISFACTION

ESTROGENS (permitting)

TESTOSTERONE (initiating)

PROGESTERONE & its metabolites (receptivity)

BRAIN

SEXUAL DYSFUNCTION

ESTROGENS

TESTOSTERONE

PROGESTERONE

SENSATIONS

SEXUAL DYSFUNCTION

VASOCONGESTION & LUBRICATION

RE Nappi, 2007
"DOMINO" EFFECT OF MENOPAUSAL SYNDROME

NEUROENDOCRINE SYSTEM

Sex steroids ➔ HRT ➔ [NEUROENDOCRINE SYSTEM]

Related to:
- Personality
- Female Identity
- Bodily Image
- Affective Life
- Coping Strategies
- Self-Esteem
- Relationships
- Stressful Events
- Partner’s Health
- Socio-Cultural Environment

Symptoms:
- Hot Flushes
- Irritability
- Depression
- Poor Concentration
- Insomnia
- ...
SEX HORMONES-DEPENDENT SEXUAL CIRCUITRIES AT MENOPAUSE

Loss of Ovarian Cyclicity

- Estrogens, Progesterone & Androgens Changes

NEUROENDOCRINE ADAPTATION

- Rearrangement of Neurotransmitters/ Neuromodulators
- Desire, Central Arousal, Pleasure, Satisfaction

VAGINAL/GENITAL PLASTICITY

- Reduced epithelial cell proliferation
- Vascular remodelling
- Diminished smooth muscle content
- Changes in innervation
- Peripheral Arousal, Orgasm

MOOD

ENGORGEMENT LUBRICATION SENSITIVITY

RE Nappi, 2006
MENOPAUSE AFTER BREAST CANCER: A SURVEY ON BCS

A questionnaire-based survey on 250 breast cancer patients (144 in postmenopause and 106 in premenopause at time of diagnosis) to determine the prevalence of menopausal symptoms and attitudes towards HRT and other treatments.

Adjuvant therapy with tamoxifen or tamoxifen plus chemotherapy is associated with a significant worsening of menopause-related symptoms of postmenopausal women.

The incidence of vasomotor and dystrophic symptoms is significantly higher in premenopausal women treated with chemotherapy and/or hormonotherapy as compared with postmenopausal women (P<0.000 and P=0.02, respectively).

Premenopausal women are more concerned about risk of breast cancer recurrence than older women and at the same time are significantly more worried about the impairment of the quality of life due to adjuvant therapy (P=0.005). Younger women are more prone to consider HRT than postmenopausal women (P=0.05).

N Biglia et al, 2003
ASSOCIATION OF BREAST CANCER & ITS THERAPY WITH MENOPAUSAL SYMPTOMS

Data from the Cancer and Menopause Study (CAMS), a tumor-registry-based cohort of breast cancer survivors (BCS) diagnosed before age 50.

Mean age of the participants was 50 years. The prevalence of symptoms was high.

Hot flashes occurred in
17% PREMENOPAUSAL
51% PERIMENOPAUSAL
71% POSTMENOPAUSAL

Hot flashes, vaginal dryness, and pain with intercourse were more severe in postmenopausal compared with perimenopausal BCS. Having had a transition during breast cancer treatment was associated with worse hot flash severity, independent of current menopause status.

C Crandall et al, 2004
New trends in HRT favor the lowest effective doses for symptoms relief and bone loss prevention in healthy recently menopausal women.

HRT: AN EVOLVING CONCEPT FOR THE INDIVIDUALIZED CARE

STANDARD

LOW

ULTRA-LOW

OTHER TREATMENTS: Tibolone, Androgens, SERMs, local therapies…

SYSTEMIC DOSE

RE Nappi, 2008
HRT IN WOMEN WITH AN HISTORY OF BREAST CANCER

The HABITS trial was one of several trials begun in the 1990s to evaluate the potential risk of recurrent breast cancer in women using HRT. Although it was designed to enroll at least 1300 women and to follow them for 5 years, it was stopped on Dec 17, 2003, after a median follow-up of slightly longer than two years.

Recurrent or de novo breast cancer had developed in
26 women in the HRT group
7 women in the no-HRT group.

The HABITS trial was terminated because women with a history of breast cancer allocated to receive HRT for menopausal symptoms experienced an unacceptably high risk of breast cancer compared with breast-cancer survivors allocated to best symptomatic treatment without hormones.

L Holmberg et al, 2004
HRT AFTER ENDOMETRIAL CANCER

• HRT after endometrial cancer (EMC) treatment is an uncertain subject with limited exploration among gynecologic cancer research. Because estrogen is a well-recognized etiologic factor of EMC, most physicians are probably reluctant to provide a replacement therapy, or limit its use to only a selected group of patients.

• HRT did not appear to increase the recurrence or death rates in EMC. However, most information came from retrospective studies with selection bias, or from a small prospective non-randomized study. The only randomized controlled trial of the Gynecologic Oncology Group could also not provide a definite answer regarding its safety and recommendation.

• In conclusion, on the basis of the currently available studies, HRT after EMC treatment does not appear to have an adverse effect on EMC. Nevertheless, because of a limitation of data, the physician should thoroughly consider all possible benefits and theoretical risks of recurrence or mortality in each individual to provide the best of care for their patients.

Tangjitgamol et al, 2008
HRT AFTER CERVICAL CANCER

• Association between use of HRT and cervical carcinoma has never been proven. In 120 women treated for stages I-II cervical cancer HRT showed no change either in survival or disease free survival at 5 years [Ploch, 1997].

• In a case-control study, the group of women on HRT showed an overall RR of 2.1 (95% CI, 0.95–4.6) for adenocarcinoma versus 0.85 (95% CI, 0.34–2.1) for squamous cell carcinoma. The risk was higher in case of estrogens alone: RR for adenocarcinoma 2.7 (95% CI, 1.1–6.8) versus 0.86 (95% CI, 0.26–2.8) for squamous cell carcinoma. With combined treatment the RR for adenocarcinoma was 1.1 (95% CI, 0.26–5.0) [Lacey et al, 2000].

• According to these data, treatment approach should be the same as for endometrial adenocarcinoma.
TIBOLONE & TARGET TISSUES RELEVANT TO MENTAL & SEXUAL WELL-BEING

NEUROENDOCRINE CIRCUITRIES
(Hot-flushes, Mood, Libido, Orgasm)

VAGINAL & CLITORAL TISSUES
(Sensations, Congestion, Lubrication)

ESTROGENIC & ANDROGENIC EFFECTS OF ITS METABOLITES

SR Davis, 2002
TIBOLONE in breast cancer survivors

LIBERATE
(Livial Intervention following Breast cancer: Efficacy, Recurrence And Tolerability Endpoints)

Objective: The primary outcome variable is breast cancer recurrence. Secondary study outcomes include vasomotor symptoms, bone mineral density (BMD), health-related quality of life (HRQL) and overall survival.

Design: a randomized, placebo controlled, double-blind, parallel-group study

Setting: worldwide, July 2002 - December 2004 (stopped prematurely six months before the planned trial end)

Participants: 3148 women treated for breast cancer with climacteric complaints were randomised at 245 centres in 31 countries.

Results: at a median follow-up of 3.1 years, an increased risk of recurrence with the use of tibolone (HR 1.40 [1.14-1.70]) was demonstrated. The risk for breast cancer recurrence with tibolone was more evident in women with ER-positive tumor status than in women with an ER-negative tumor status.

Kenemans et al, 2009
Breast Cancer Recurrence (ITT)
HR Tibolone to Placebo [95% CI]

HR=1.40
95% CI: 1.14-1.70

Kenemans et al, 2009
Breast Cancer Recurrence (ITT)
Estrogen Receptor status Positive (n=2185)

Number at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tibolone 2.5 mg</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>Number at risk</td>
<td></td>
</tr>
<tr>
<td>Tibolone</td>
<td>1112</td>
<td>1073</td>
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<tr>
<td></td>
<td>1023</td>
<td>984</td>
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<td>625</td>
<td>634</td>
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<td>190</td>
<td>204</td>
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</table>

Cumulative percentage

Time since randomization (days)

HR=1.56
95% CI: 1.22-2.01

Kenemans et al, 2009
Breast Cancer Recurrence (ITT)
Estrogen Receptor status Negative (n=623)

<table>
<thead>
<tr>
<th>Time since randomization (days)</th>
<th>Number at risk</th>
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<tr>
<td>0</td>
<td>39 tibolone</td>
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<tr>
<td>365</td>
<td>37 placebo</td>
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<tr>
<td>730</td>
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<td>1095</td>
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<tr>
<td>1460</td>
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HR=1.15
95% CI: 0.73-1.80

Kenemans et al, 2009
Breast Cancer Recurrence (ITT)  
HR and 95% CI by Endocrine Therapy

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<tr>
<td>TAM at BL</td>
<td>N=2068</td>
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<td>Arom.Inh. at BL</td>
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<td>GnRH analogs at BL</td>
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<td>Ovariectomy</td>
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Kenemans et al, 2009
Breast Cancer Recurrence (ITT)
Aromatase Inhibitor use at Baseline (n=202)

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<th>Treatment</th>
<th>Number at risk</th>
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<th>365</th>
<th>730</th>
<th>1095</th>
<th>1460</th>
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<tr>
<td>Tibolone 2.5 mg</td>
<td>103</td>
<td>93</td>
<td>81</td>
<td>60</td>
<td>15</td>
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<tr>
<td>Placebo</td>
<td>99</td>
<td>84</td>
<td>80</td>
<td>60</td>
<td>16</td>
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</tr>
</tbody>
</table>

Status at baseline

HR=2.42
95% CI: 1.01-5.79

Kenemans et al, 2009
Breast Cancer Recurrence (ITT)
Tamoxifen use at Baseline (n=2068)

Number at risk

<table>
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<tr>
<th>Treatment</th>
<th>0.00</th>
<th>0.05</th>
<th>0.10</th>
<th>0.15</th>
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<th>0.25</th>
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<tr>
<td>Tibolone 2.5 mg</td>
<td>1037</td>
<td>955</td>
<td>880</td>
<td>581</td>
<td>185</td>
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<tr>
<td>Placebo</td>
<td>1031</td>
<td>943</td>
<td>866</td>
<td>587</td>
<td>188</td>
<td></td>
</tr>
</tbody>
</table>

HR=1.25
95% CI: 0.98-1.59

Kenemans et al, 2009
APHRODITE
(Transdermal Testosterone Patch Only)

Study Design

• Randomized, double-blind, multinational study over 12 months
  - Placebo or 150mg/day or 300mg/day transdermal testosterone patch given twice weekly

• Efficacy assessed through 24 weeks in 4-week frequency

• Hormone levels, adverse events and clinical labs evaluated over 12 months

• 814 postmenopausal women with HSDD were enrolled
  - 771 (95%) participants were included in the 24 week efficacy analysis

S Davis et al, 2008
RESULTS: At 24 weeks, the increase in the 4-week frequency of satisfying sexual episodes was significantly greater in the group receiving 300 microg of T per day than in the placebo group (an increase of 2.1 episodes vs. 0.7, P<0.001) but not in the group receiving 150 microg/day (1.2 episodes, P=0.11). The rate of androgenic adverse events - primarily unwanted hair growth - was higher in the group receiving 300 microg of T per day than in the placebo group (30.0% vs. 23.1%). Breast cancer was diagnosed in four women who received T (as compared with none who received placebo); one of the four received the diagnosis in the first 4 months of the study period, and one, in retrospect, had symptoms before undergoing randomization.

CONCLUSIONS: In postmenopausal women not receiving estrogen therapy, treatment with a patch delivering 300 microg of testosterone per day resulted in a modest but meaningful improvement in sexual function. The long-term effects of testosterone, including effects on the breast, remain uncertain.

S Davis et al, 2008
TOPOICAL USE OF HORMONAL & NON-HORMONAL PRODUCTS FOR FSD AT MENOPAUSE

- CEE/Estriol/other weak estrogen cream
- Estradiol tablets or ring
- Testosterone Cream
- Lubricants/Gels

Local treatments improve the genital response but they do not directly affect the motivational aspects of sexual function & behaviour.
Addressing sexual issues early in the disease trajectory may prevent or minimize subsequent negative effects.

INDIVIDUALIZED COUNSELLING

TAILORED MANAGEMENT

QUALITY OF LIFE

RE Nappi, 2005