Menopause, Hormones and Sexuality

with focus on iatrogenic PM

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for the cure and care of pain in women

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Conflict of interest 2013-14

• Speaker:
  Abbott, Bayer, Deakos, LoLipharm, Menarini, Pfizer

• Advisory Board:
  Bayer, Menarini

• Consultant:
  Abbott, Bayer, Deakos, Epitech, LoLipharm, Menarini, Pfizer, Zambon
Graziottin A.
Menopause and sexuality:
key issues in premature menopause and beyond

Lukasiewicz M & Graziottin A.
Sexuality after gynecological cancers
In Chervenack F. Studd J. Progress in Obstetrics and Gynecology, 2014
Epidemiology of premature menopause

- POF: 1%\(^1\) to 7.1%\(^2\) of women under 40
  
  1.0% Caucasian, 1.4% African American, 1.4% Hispanic,
  0.5% Chinese, 0.1% Japanese (SWAN study) \(^1\)

  1) Luborski et Al, Hum Reprod, 2003; 2) Adamopoulos et Al, Menopause, 2002

- Iatrogenic
  
  3.4%\(^3\) to 4.5%\(^4\) under 40
  11.7%\(^1\) between 40 and 45

Health expectancy and life expectancy

Life Expectancy in Italy: 84.5 yrs
CIA World Factbook, 2012

Health Expectancy 70 yrs

Shorter Health Expectancy in women with Iatrogenic PM after cancer

HE GAIN with lifestyles + HRT

+ years of disease - health expectancy

A.Graziottin, 2014
Question 1. Which are the key challenges in oncology today?

1. Improve survival rates
2. Increase the disease free survival
3. Tailor treatment according to cancer subtypes AND women’s subgroups

Increase HEALTH expectancy Including sexuality

A. Graziottin, 2014
Key points

1. Estrogens and sexual hormones
2. Premature menopause (PM): key issues
3. Neuroinflammation, depression and sickness behaviour after surgery/chemotherapy/RT and PM

With focus on the biological issues

Lukasiewicz & Graziottin Sexuality after Gynecological cancers, In Chervenak & Studd eds: Progress in Obstetrics and Gynecology, 2014
Question 2.

How should we read the estrogenic scenario?

Focus on:
1. types of estrogens
2. estrogenic receptors alfa e beta
3. agonist or antagonist actions
4. levels of estrogens

A. Graziottin, 2014
Natural human estrogens

AND a **synthetic** estrogen: promestriene
Estrogenic receptors: 2 types

- **alpha** and **beta**

  - **alpha** are mostly localized in the hypothalamus, breast and genitals
  - they mediate the \textit{proliferative} actions

  - **beta** are present in almost all tissues & organs
  - they mediate the \textit{reparative} and \textit{antiproliferative} actions

A.Graziottin, 2014
Estrogens and women’s health

Estrogens are *trophic* for ALL organs and tissues

Symptoms induced by PM and loss of estrogens depend on an organ/tissue vulnerability genetically determined

A. Graziottin, 2014
Estrogenic receptor alpha: AGONIST action with ESTRADIOL

courtesy of Prof. Jan-Ake Gustaffson, 2002
Estrogenic receptor alpha: ANTAGONIST action with RALOXIFENE

ER–α LBD
RAL-induced conformation

Hydrophobic cleft formed between H3 and H5
Helix 12
Lys 362 – coactivator binding?

Charged amino acids on H12
H# – helices that interact with H12

courtesy of Prof. Jan-Ake Gustaffson, 2002
## Levels of estrogens in women

<table>
<thead>
<tr>
<th>Life phase</th>
<th>Estrogenic levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertile age</td>
<td>50-100 pg/mL in post menstrual phase</td>
</tr>
<tr>
<td></td>
<td>400-600 pg/mL at ovulation</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>40,000 pg/mL at term</td>
</tr>
<tr>
<td>Menopause</td>
<td>5-30 pg/mL natural</td>
</tr>
<tr>
<td></td>
<td>unchanged with vaginal promestriene, estriol or estetrol</td>
</tr>
<tr>
<td></td>
<td>25-50 pg/mL with systemic HRT</td>
</tr>
</tbody>
</table>

A.Graziottin, 2014
# Mean Steroid Levels in Women

Values converted to pg/mL

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Reproductive age</th>
<th>Natural Menopause</th>
<th>Iatrogenic Menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>100-150</td>
<td>10-15</td>
<td>10</td>
</tr>
<tr>
<td>Testosterone</td>
<td>400</td>
<td>290</td>
<td>110</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>1900</td>
<td>1000</td>
<td>700</td>
</tr>
<tr>
<td>DHEA</td>
<td>5000</td>
<td>2000</td>
<td>1800</td>
</tr>
<tr>
<td>DHEAS</td>
<td>3,000,000</td>
<td>1,000,000</td>
<td>1,000,000</td>
</tr>
</tbody>
</table>

Lobo R. 1999
Central Effects on Sexual Function

- Estrogen (permissive)
- Testosterone (initiation)
- Progesterone (receptivity)

SUBJECTIVE EXCITEMENT

- Desire
- Subjective excitement
- Orgasm

- Prolactin
- Oxytocin
- Endorphins
- Adrenaline
- Thyroid

Dopamine (DA)
Norepinephrine (NE)
5-HT

Modified from Clayton AH. *Psychiatric Clinics of North America*. 2003;26:673-682
Peripheral Effects on Sexual Function

Gonads & adrenals

- Estrogen
- Testosterone
- Progestin

Maintain genital structure and function

SENSATION

Clitoral and penile tissue

VASOCONGESTION

5-HT

Nitric Oxide (NO)

5-HT$_{2A}$

NE

VIP

Prostaglandin E

Clayton AH. 2003

5-HT

NPY

Substance P

Cholinergic fibers

Clitoral and penile tissue

Estrogen

Testosterone

Progestin

Maintain genital structure and function
Female Sexual Function

MOOD

SEXUAL DESIRE & CENTRAL AROUSAL

RESOLUTION & SATISFACTION

ORGASM

GENITAL AROUSAL & LUBRICATION

Feedbacks from the genitals

Systemic ANDROGENS

Systemic ESTROGENS Progestins

Topical Estrogens & Androgens

A. Graziottin, 2014
Question 3.

What are the leading symptoms in young women with cancer and iatrogenic premature menopause?

Lukasiewicz & Graziottin Sexuality after Gynecological cancers, In Chervenak & Studd eds: Progress in Obstetrics and Gynecology, 2014
What is the HEALTH’ PRICE of an early and symptomatic menopause?

<table>
<thead>
<tr>
<th>Duration</th>
<th>System</th>
<th>Symptoms/disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Neuroendocrine</td>
<td>Hot flushes, Night sweats, Insomnia</td>
</tr>
<tr>
<td>Months</td>
<td>Neuroinflammation</td>
<td>Mood changes, Anxiety, Irritability, Loss of memory</td>
</tr>
<tr>
<td></td>
<td>Genital tract</td>
<td>and concentration</td>
</tr>
<tr>
<td>Months</td>
<td>Arterial</td>
<td>Genital tract atrophy, Dyspareunia</td>
</tr>
<tr>
<td></td>
<td>Genital aging</td>
<td>Loss of libido, Urethral syndrome</td>
</tr>
<tr>
<td>Years</td>
<td>Joint</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Chronic</td>
<td>Skeletal</td>
<td>Ostheoarthritis, Osteoporosis, Related fractures</td>
</tr>
</tbody>
</table>

Modified from Whitehead, 2004
Symptoms of Estrogen and Androgen Loss

- **Short-Term Symptoms**
  - Mood, sleep, and/or acute cognitive changes
  - Night tachycardia
  - Sleep disorders
  - Hot flushes
  - Urogenital symptoms
    - Decreased Sexual Activity
    - Decreased Arousal
    - Decreased Libido

- **Long-Term Symptoms**
  - Estrogen Secretion:
    - 40
    - 45
    - 50
    - 55
    - 60
    - 65
    - 70
    - ≥75

**Onset**
- Insidious
- with significant individual variability

Modified from JL Alexander, www.afwh.org
Thermogram of a Hot Flush

Courtesy of M. Whitehead, 2004
Severity of hot flushes

Neurobiological marker of neuroinflammation and brain vulnerability to loss of estrogens & ageing: depression, Alzheimer, Parkinson

A. Graziottin, 2014
The first neglected biological marker

1) Age at menopause

- The earlier the menopause the more aggressive the impact on general health, brain aging and sexual ageing

unless appropriate Hormonal Treatment is given, when not contraindicated, until the age of 51

EMAS, IMS, NAMS consensus conferences on HT

A.Graziottin, 2014
### Table 2

Cohort analyses for women who underwent either unilateral or bilateral oophorectomy and for referent women in Olmsted County, MN

<table>
<thead>
<tr>
<th>Cohort or stratum</th>
<th>Women at risk</th>
<th>Follow-up (person-years)</th>
<th>Women with cognitive impairment or dementia</th>
<th>Unadjusted hazard ratio (95% CI)†</th>
<th>p</th>
<th>Adjusted hazard ratio (95% CI)†</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referent women</td>
<td>1,472</td>
<td>39,044</td>
<td>98</td>
<td>1.0 (ref.)</td>
<td>—</td>
<td>1.0 (ref.)</td>
<td>—</td>
</tr>
<tr>
<td>Any oophorectomy</td>
<td>1,489</td>
<td>40,736</td>
<td>150</td>
<td>1.45 (1.12-1.87)</td>
<td>0.005</td>
<td>1.46 (1.13-1.90)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age at surgery, y†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (&lt;38)</td>
<td>529</td>
<td>15,713</td>
<td>28</td>
<td>2.79 (1.81-4.31)</td>
<td>&lt;0.0001</td>
<td>2.89 (1.86-4.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T2 (38-45)</td>
<td>432</td>
<td>11,909</td>
<td>43</td>
<td>1.57 (1.09-2.25)</td>
<td>0.01</td>
<td>1.54 (1.06-2.23)</td>
<td>0.02</td>
</tr>
<tr>
<td>T3 (&gt;45)</td>
<td>528</td>
<td>13,114</td>
<td>79</td>
<td>1.19 (0.88-1.61)</td>
<td>0.25</td>
<td>1.22 (0.90-1.65)</td>
<td>0.21</td>
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<tr>
<td>T1 + T2 (≤45)</td>
<td>961</td>
<td>27,622</td>
<td>71</td>
<td>1.88 (1.38-2.56)</td>
<td>&lt;0.0001</td>
<td>1.88 (1.37-2.58)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Indication for surgery§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign conditions</td>
<td>941</td>
<td>26,867</td>
<td>86</td>
<td>1.47 (1.10-1.97)</td>
<td>0.009</td>
<td>1.46 (1.08-1.96)</td>
<td>0.01</td>
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<tr>
<td>No specified indication§</td>
<td>548</td>
<td>13,869</td>
<td>64</td>
<td>1.42 (1.03-1.94)</td>
<td>0.03</td>
<td>1.47 (1.06-2.02)</td>
<td>0.02</td>
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<tr>
<td>Analyses including a broader definition of cognitive impairment§</td>
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<td></td>
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<td>1.34 (1.05-1.71)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Rocca et al, Neurology, 2007*
Key mental symptoms in young Cancer patients with PM1.

Estrogenic loss:
- Ovariectomy & hysterectomy
- chemotherapy and PM
- PM/M
- NEUROVEGETATIVE disruption
  - insomnia, poor sleep quality, nicturias
  - hot flashes/ sweatings /tachycardia
  - fatigue
  - loss of sex drive, poor arousal

Lukasiewicz & Graziottin, Progress in Obstetrics 6 Gynecology, 2014
Key symptoms in young cancer patients with PM 2.

- AFFECTIVE disruption
  - depression
  - anxiety

- COGNITIVE impairment
  - memory loss
  - difficulty in decision making
  - coping difficulties
  - professional impairment

Lukasiewicz & Graziottin, In Chervenak and Studd (Eds); Progress in Obstetrics and Gynecology, 2014
Hot flushes: somatic, cognitive and emotional correlates

Courtesy of M. Whitehead, 2004
What is the common denominator of so many symptoms?

Systemic and neuro inflammation!

Lukasiewicz & Graziottin Sexuality after Gynecological cancers,
In Chervenak & Studd eds: Progress in Obstetrics and Gynecology, 2014
Graziottin et Al. J.Depression & Anxiety, 2013
Graziottin et Al, Gynecol Endocrinol, 2014
INFLAMMATION = TO SET ON FIRE

a biochemical fire, involving mastcells, tissues, cytokines, nerves and neurons, microglia = neuroinflammation with sickness behaviour and depression & ...loss of libido

Graziottin et Al, J Depression & Anxiety, 2013
Graziottin et Al, Gynecol. Endocrinol, 2014
THE UP-REGULATED MASTCELL

Menstrual blood in the tissue

Mechanical trauma

Intercourse!!!

Neurogenic stimulus & neurotrophic changes

Bohme-starke, 1998, 2010;
Moigui 2009;
Costigan 2010, Graziottin et Al, 2013, 2014

FLUCTUATION LOSS/ Estrogens

Chemical & Physical insults

Infections

Chemical & Physical insults

Infections

Agonist stimuli

Tumor growth

Cell death

NERVE GROWTH FACTOR (x 50!)

Dupont et Al, 2001

Cytokines

Serotonine

Hystamine

Vasoactive factors

Bradychinine

Mechanical trauma

Intercourse!!!

Neurogenic stimulus & neurotrophic changes

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Dupont et Al, 2001

Cytokines

Serotonine

Hystamine

Vasoactive factors

Bradychinine
Fire! A mast cell ejects a load of histamine near a blood vessel

Nautiyal et al. PNAS (2008)
The mast cell: A "single cell gland"

Nautiyal et al. www.pnas.org/cgi/content/short/0809479105
Balance of inflammation

Pro-inflammatory and neurotoxic factors

- TH1 cytokines
  - TNFα
  - IL-1
  - S100β
  - NO
  - ROS
  - Glutamate
  - Leukotrienes
  - Chemokines

Anti-inflammatory and neuroprotective factors

- TH2 cytokines
  - TGF
  - Soluble TNF receptor
  - Soluble IL-1 receptor
  - IL-1 receptor antagonist
  - BDNF
  - NGF
  - NT-3
  - GDNF

Diseased brain

Effect of risk factor genes

Healthy brain

Neurodegeneration

Neuroregeneration

S.Skaper, 2014
Inflammation is a key feature in (young) Cancer patients

Triggers:

- Estrogen loss
- Surgery/Chemotherapy /RT cell destruction
- Emotional stress with CRP activation

Systemic inflammation

Nervous inflammation

Sickness behaviour
Depression
Sexual Symptoms

A.Graziottin, 2014
Why and when is depression affecting young cancer patients with PM? Is is psychological or are there biological correlates?
Timing and overlap of sickness and acute pain with depression and chronic pain.


Inflammation is clearly the common denominator to both pain and depression, initiating the activation of several pathways that can trigger the transition from sickness to depression and from acute to chronic pain.

Understanding neuroimmune mechanisms that underlie depression and pain comorbidity may yield effective pharmaceutical targets that can treat both conditions simultaneously beyond traditional antidepressants and analgesics.
Sickness behaviour

It is a set of coordinated **physiological and behavioural** changes in response to **systemic inflammation**: fever, malaise, social withdrawal, fatigue, myalgia, loss of appetite.

When **inflammation, tissue damage and pain persists**, the sickness behaviour becomes maladaptive and contributes to depression and further pain.

Roman et Al. Pharmacol Res. 65 (6): 1663-72, 2013
Neuronal activity triggers neurogenic inflammation in peripheral tissues.
Neuronal activity triggers neurogenic neuroinflammation in the CNS.
Glia and immune cell signaling

Microglia: The key cells where actions of antidepressants and mood stabilizers converge

Stress
Systemic Infection
Medical Illness
Neuroendocrine Disease

↑ IL-1β
↑ TNFα
↑ iNOS
↑ C-RP

Activated Microglia

Cytokine production

Immune-Brain Barrier

Tryptophan

↑ IDO

↓ 5-HT

↑ Quinolinic acid

↓ BDNF

↓ GSK3-β

Astrocyte

↑ TNFα
↑ NFκB/Map38
*apoptosis
Δ neuronal plasticity & neurogenesis

↑ excitotoxicity

↑ glutamate

Neural Behavioral Impairments

MOOD
SLEEP
ENERGY
CONCENTRATION
COGNITION

Citation: Transl Psychiatry (2014) 4, e350; doi:10.1038/tp.2013.119
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www.nature.com/tp
Female Sexual Function

Level of systemic and neuroinflammation

MOOD

SEXUAL DESIRE & CENTRAL AROUSAL

RESOLUTION & SATISFACTION

MOOD

GENITAL AROUSAL & LUBRICATION

ORGASM

Feedbacks from the genitals

Systemic ANDROGENS

Systemic ESTROGENS

Progestins

Topical Estrogens & Androgens

A. Graziottin, 2014
Women are never too young to get menopausal

The younger the age, the more severe the impact on health and sexuality

Inflammation is the common denominator

Estrogen loss, cancer & cancer therapy worsen inflammation and depression
listen to your patients and raise the sexual issues it’s difficult to provide an effective intervention if there is no mention of a problem

And offer a well tailored HRT when oncologically feasible!

A. Graziottin, 2014
“Yes, I’m alive, but my life is longing”

Goal: My passion for life & love is back again!