MENOPAUSE,
PERIMENOPAUSE,
POSTMENOPAUSE.

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Plan

- General considerations about aging
- Definitions
- Endocrinology of the perimenopause
- Endocrinology of the menopause
- Estrogen Deficiency
  - Symptoms and signs
  - The Brain
  - The Bones
  - Cardiovascular system
Aging

- 1650 mio of human being in 1900
- 6168 mio of human being in 2000

- In the next 25 years in western countries
  - People over 65 will increase from 82 %
  - Newborn will increase from 3 %
  - People 20 to 65 will increase from 46 %
Aging and Quality of Life

• There is some interest to maintain our old population in good health, by
  – exercise
  – stop smoking
  – not much of alcohol
  – control obesity

  – Good Quality of Life allows Choices
**Definition**

- **Menopause:** permanent cessation of menstruation following the loss of ovarian activity. 12 months.
- **Median age:** 50 to 52 years old
- **Post hysterectomy:** FSH > 30-60 U/l
• **Perimenopause:**
  – Period of time where a woman passes from the reproductive stage of life to the menopause.
  – May starts about 8 years before menopause.
  – Marked by irregular cycles and climacteric symptoms.
From the endocrinologic point of view

- Menopause is the end point of a process.
  - Hormones are stable
  - Take care of the long term consequences of hypoestrogenism.

- Perimenopause is an ongoing process
  - Hormones are fluctuating
  - Key word is “variability”
  - Take care of the short term consequences
Premature ovarian failure

- POF = before 40 years old

- Many causes:
  - Genetics: premutation of chrom. X
  - Enzymatic
  - Physical agents (radiotherapy; anticancer)
  - Immunologic
  - Failure of FSH/LH
  - Idiopathic
Premature menopause (POF)

- Age of menopause genetically determined (X chromosome)
- Dx made by hormonal profile
- Ovarian volume (ultrasound) may distinguish simple POF from insensitive ovary syndrome ("immunological")
The Endocrinology of the Perimenopause
Physiology of the menstrual cycle

- D1-D14: follicular phase
- D14: ovulation
- D14-D28: luteal phase
- Ovarian secretion
- Adrenal secretion

- FSH ➔ / E2 ➔
- LH ➔/ A ➔/ T ➔
- P ➔ / E2 ➔
- E2,E1, P, A, DHEA, T
- DHEAS,DHEA, A➔T
Regular menstrual cycle

- Related to the number of ovarian follicles
- Reduction by atresia
  - 7 mio of oocytes at 20 weeks of gestation
  - 2.5 mio of follicles at birth
  - 400 000 at the time of menarche.
- Necessity of normal hypothalamus, pituitary gland, ovary, cortex, thyroid and adrenal
Perimenopause

- Age related alterations start at approximately 42-44
- Ovarian production of proteins affected first (clinically silent)
- Ultimately, ovulation disorders result in dysfunctional breakthrough bleeding (Pre/peri-menopause)
- DUB may be associated with hyperplasia
Perimenopausal transition

- Decreased stocks of ovarian oocytes
- Decreased Inhibin
- Ovulation/Anovulation
- FSH ↑
- Normal E2 - P or E2 ↑, normal P or E2/P ↑
The Endocrinology of the Menopause
Menopause and hormonal modifications

- Postmenopausal hormonal profile:
  - FSH > 30 U/l
  - LH > 15 U/l
  - E2 < 40 pg/ml

- Ovarian production:
  - T stays unchanged, DHEA and A decrease

- Adrenal production:
  - Decreased DHEA and A
Source of estrogen at the postmenopause

- Not from the ovary

- From peripheral conversion in the adipose tissue
  - Androstenedion to Estrone
  - Testosterone to Estradiol
Hormone Measurements

- Not helpful when menopause occurs at expected age
- Reflect instant status, fluctuate a lot
- Hormonal profile helps to clarify premature symptoms
- Can not accurately predict fecundity
- Ovarian volume (ultrasound) is helpful
Estrogen Deficiency

Symptoms and signs
Brain
Cardiovascular system
Bone
Symptoms and Signs

- Hot Flashes
- Psychological functioning
- Vulvovaginal and urinary disorders
Incidence of Hot Flusches

Mayas Indians: 0 %
Chineses from Hong Kong 10-22 %
Japanese: 17 %
North American 45 %
Netherlands 80 %

Research on the menopause in the 1990s
Technical report of a WHO Scientific group
No 866, 1996
Hot Flashes (HF)

- Emblematic symptom for menopause
- Episodic phenomenon with:
  - upper body vasodilatation
  - intense perspiration
  - unpleasant psychological symptom(s)
- Up to one every 60 minutes, timely related episodic LH elevations
- Only after prior exposure to E2
- Aggravated by hot climate
Hot Flashes (HF)

- Episodic resetting of thermostat after progressive upward slide of Basal Body Temperature (BBT) reference
  - Ends when BBT reaches new lower setting
Psychological functioning

- Depressive symptoms
- Memory difficulties
- Concentration difficulties
- Sleep disorders
- Decrease of sexual interest
  - 30-50 % of the general menopausal population
Psychological Functioning

- Natural menopause doesn’t increase the risk of depression (*longitudinal studies*)
  
  *Kaufert PMaturitas 1992; 14: 143*

  However

- 65% of women attending “menopause clinics” had varying degrees of depression
  
  *Anderson E Am J Obstet Gynecol 1987; 156:428*
Effect of estrogen deficiency on the urogynecologic mucosa

- Vaginal atrophy leading to vaginal dryness
- Urethral mucosa atrophy leading to pollakiuria
- Bladder mucosa atrophy leading to urge incontinence
Incidence of urinary incontinence

- Depending on what population is studied
- Walking in clinics:
  - 489 women 50-64 yo 30%
  - 285 women attending “menopause clinics”:
    - 45% stress
    - 21% urge

Hoyte L. Management of the menopause 2000

- Female Nursing home residents 50%
Vulvovaginal and urinary disorders

Effects of Estrogens

E receptors found on urethral and bladder mucosa

E2 increase elasticity by collagen synthesis
Effects of sex steroids on the Brain

- For reproductive functions
  - Neuroendocrine hormone release
  - Behavior

- For non reproductive functions
  - cerebral lateralisation
  - response of the brain to injury
  - cognitive performances
Neurobiologic effects of Estrogens

- **Direct**
  - alteration of the electrical activity of the hypothalamus

- **Inductive**
  - induction of the RNA/protein synthesis ➔ changes in a specific gene product, such as neurotransmitter synthesizing enzymes.
Where to find Estrogens receptors

Pituitary
Hypothalamus ( ERα / ERβ )
Limbic Forebrain ( ERα > ERβ )
Cerebellum ( ERβ )
Cerebral Cortex ( ERα > ERβ )
Brain Stem
Spinal Cord
The Brain

**Effects of Estrogens**

Increase synaptic density in the hippocampus (limbic sys. structure for memory)

Increase neurotransmitters activity (acetylcholine)

Increase the rate of degradation of MAO

Stimulate neurons growth ➔ reparation

Act as an antioxydant
Effect of estrogen deficiency on the CNS

- Hot flushes
- Sleep disorders
- Loss of memory
- Fatigue
- Irritability
Estrogen Deficiency
and
The Bones
Bone mass and osteoporosis

- Bone: constant remodeling
- Bone mass reflected by: bone formation, bone resorption
- Remodeling is important in:
  - Maintaining the vitality of the skeleton
  - Maintaining the capacity to resist stress
  - Contributes to calcium homeostasis
Definition

- **Osteoporosis**
  - Bone mass below the range expected in young healthy adult (20-30 years old) of the same sex.
  - Statistically, BMD more than -2.5 SD from the peak bone mass.
Estrogen deficiency and Bone

- Gonadal failure increases bone resorption
  - More remodeling sites are activated
  - More bone is removed than synthesized

- Biochemical markers of the bone remodeling increased in urine:
  - Desoxypiridinoline, Hydroxyproline, Calcium

- Bone loss leads to osteoporosis
Estrogen deficiency and Bone

- Bone loss occurs at a rate of 2 to 3 % per year in early menopause
- Bone loss continues during the next years
- Bone loss accelerates in older age

- Decreased intestinal absorption of Calcium
- Increased renal loss of Calcium
Where to find Estrogens receptors

- Osteoblasts
- Osteoclasts
- Mononuclear cells
Estrogen Deficiency and Cardiovascular Disease
Coronary Heart Disease (CHD)

- Lower CHD incidence in women before menopause
- After menopause, similar CHD incidence in men and women
- Ovarian function protects against CHD
Effects of Estrogen on Coronary Artery

- Animal Model studies provided indirect evidence regarding the effects of endogenous sex hormones on atherosclerosis extent.

*Adam MR Atherosclerosis 1985; 5:192-200*
Animal studies: coronary plaque extent in four groups of cynomolgus monkeys model
Effects of Estrogen on Lipoprotein Metabolism

- On LDL-lipoprotein
  - Increased catabolic rate of LDL
  - Increased hepatic receptors of LDL

- On HDL-lipoprotein
  - Increased HDL-lipoprotein synthesis
  - Decreased HDL clearance
  - Reduced hepatic receptors of HDL
Effects of Estrogen Deficiency on Lipid profile

- Increased total cholesterol (CHOL)
- Increased Low density lipoproteins (LDL)
- Increased triglycerides (TG)


- Decreased High density lipoprotein (HDL)

⇒ MORE ATHEROGENIC
Effects of Estrogens on the Arterial Circulation

- Estrogen receptors on
  - endothelial cell
  - on smooth muscle cells
- Vascular relaxation on
  - Coronary arteries
  - Peripheral: brachial, carotid arteries
  - Cerebrovascular arteries
Effects of Estrogens on Coronary Endothelium

- Ach-induced vasoconstriction is abolished by an infusion of E2; gender dependent.
  - Collins P Circulation 1995; 92: 24

- This effect is caused by NO.
  - Guetta V Circulation 1997; 96: 2795

- This effect may be dependent on ERα.
  - On cultured human umbilical, aortic, coronary endothelial cell.
    - Venkov CD Circulation 1996; 94: 727
Effects of Estrogen on Coronary Smooth Muscle cells

- In vitro and animal studies

- Supraphysiologic concentration of E2 (> 0,1 µmol/L)

- Mediated by potassium or calcium channel

_Sudhir K J Am Coll Cardiol 1995 ; 26 (3):807_
Estradiol (E2) and Coronary Heart Disease (CHD)

- Oral E2 increases HDL and lowers LDL
- E2 induces direct vasoactive effects (NO and non-NO mediated)
- E2 decreases smooth muscle proliferation
- E2 improves vascular reactivity
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Conclusions

• Menopause is a physiologic event.
  – women who are not symptomatic don’t seek medical advice.

• Menopause coincides with middle age
  – increased incidence of CHD
  – increased incidence of cancer
  – increased incidence of osteoporosis
Conclusion

- Estrogen deficiency is responsible for
  - alteration of the quality of life by
    - alteration of mood disorders
    - sleep disorders
    - urogynecologic symptoms
  - osteoporosis
  - more atherogenic lipid profile
Conclusion

- Estrogen deficiency may be responsible for
  - Increased incidence for CHD
  - Decreased cognitive function
  - Decreased memory

- Is Estrogen deficiency responsible for
  - Alzheimer disease?
  - Parkinson disease?
Conclusion

● Menopause is the opportunity for women
  – to be screened for age related diseases
    ● cardiovascular risks factors
    ● cancer
    ● osteoporosis

  – to receive medical advise about health care