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 smocking
  - 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

Definition

- **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 hypoestrogenisme.
- Perimenopause is an on going 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

- FSH ↗↘ / E2 ↗↗
- LH ↑↑/ A ↗/ T ↗
- P ↗↘ / E2 ↗↘

- Ovarian secretion
- Adrenal secretion

- E2,E1, P, A, DHEA, T
- DHEAS,DHEA, A→T

Regular menstrual cycle

- Related to the number of ovarian follicules
- Reduction by atresia
  - 7 mio of oocytes at 20 weeks of gestation
  - 2.5 mio of follicules 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

- FSH ↗

- Ovulation/ Anovulation

- 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 %
Japaneses	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 squeleton
  - 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 intestin 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)

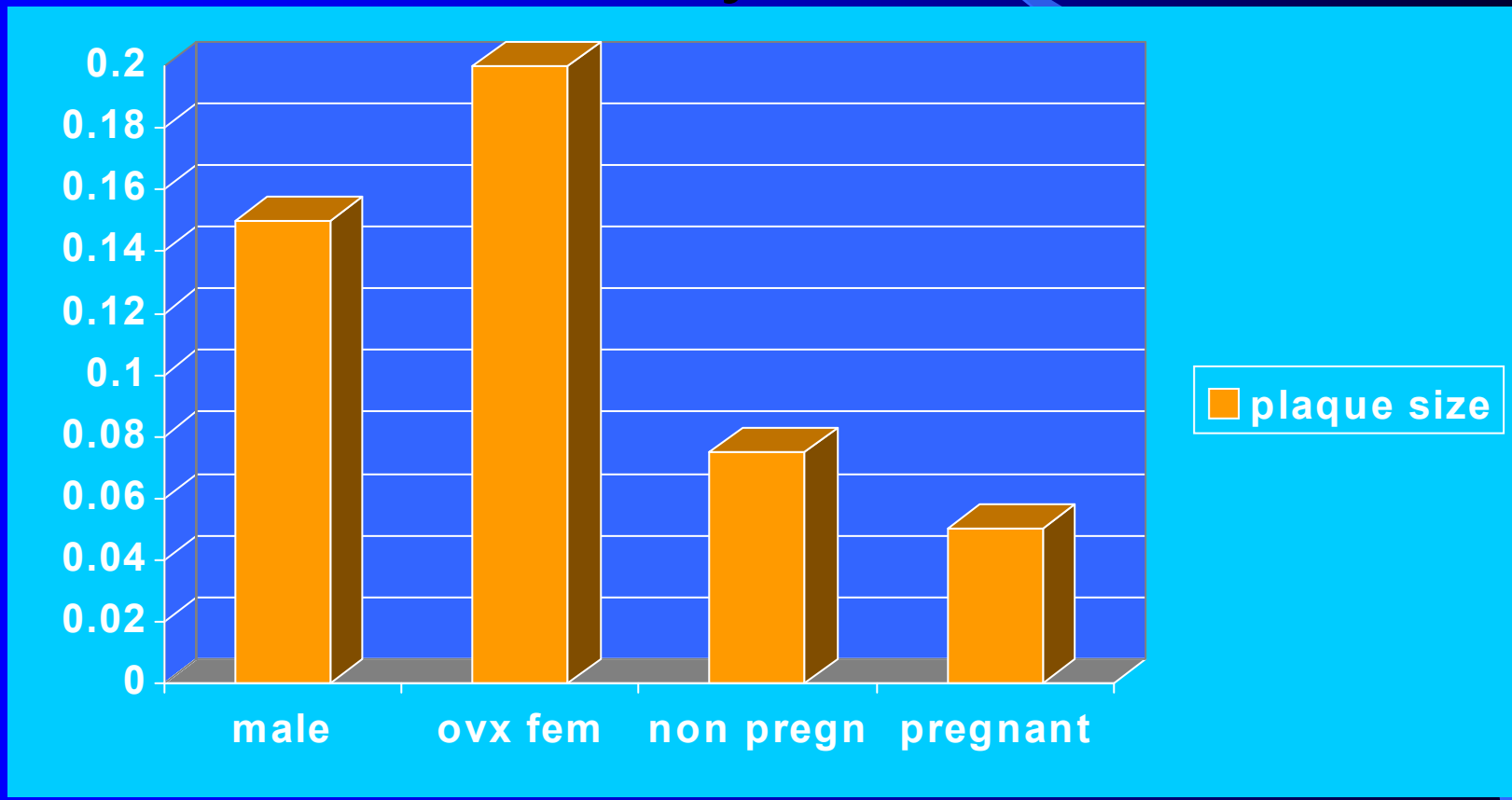
- Lower CHD incidence in women before menopause
- After menopause, similar CHD incidence in men and women
- Ovarian function protects against CHD

Effects of Estrogen on Coronary Artery

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

Adam MR Atheroscerosis 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)

Matthews KA N Engl J Med 1989; 321 641

- 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 ombilical, 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
    - uroggynecologic symptoms
  - osteoporosis
  - more atherogenic lipid profile

Conclusion

- Estrogen deficiency may be responsible for
  - Increased incidence for CHD
  - decreased cognitive fonction
  - 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**