The menopause
(here and today)

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What is menopause ?

- **The end of periods**
- **The end of the ovarian activity**
- **The end of reproductive capacity**
- **The transition from childbearing years to non-childbearing years**

- ***The term derives the Greek words menos (month) and pausis (pause)***

Perimenopause

- The term defines the period that precedes (pre-menopause) and follows menopause (post-menopause)
- Is characterised by progressive decrease in ovarian function and the appearance of the clinical and biological signs associated to this event
- Can last several years and must be related to the concept of life expectancy

Epidemiology of menopause

- Mean age of menopause varies according to studies
- MWHS : 51.3 years
- Mostly between 48 and 52 years
- 90% of women are menopaused between 45 and 55 years of age
- Mean age at perimenopause : 47.5 years of age
- Duration of postmenopause : life expectancy is 33 years after the age of 50.

Where does the aging process start?

- Endocrine mechanisms
- Ovarian reserve
- Oocyte quality
- Implantation

Changes

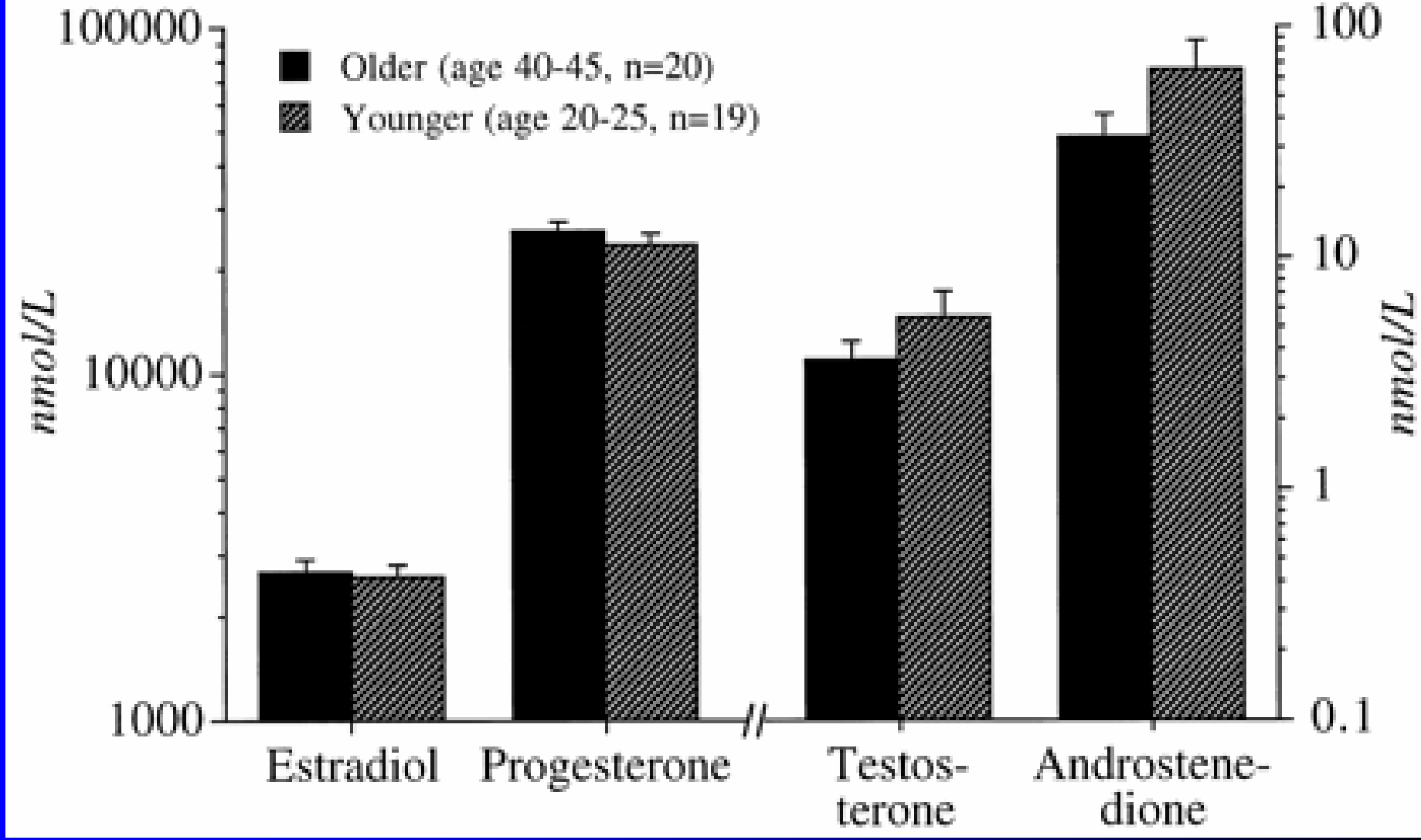
- **Already 10 years before menopause slight changes in menstrual cycles can be discerned.**
  - Follicular phase shortens and hence does the menstrual cycle.
- A progressive **rise in FSH** secretion has been described throughout reproductive life and accelerates approximately a decade before menopause and therefore concedes with a phase of accelerated follicle depletion.

Changes

- Aging of oocytes (starts in uterus)
- Decrease of the oocyte reserve (25000) by the age of 37.5y old
- Critical threshold 1000 oocytes (51 y)
- Aging of the granulosa cells
- Aging of ovarian vascular system

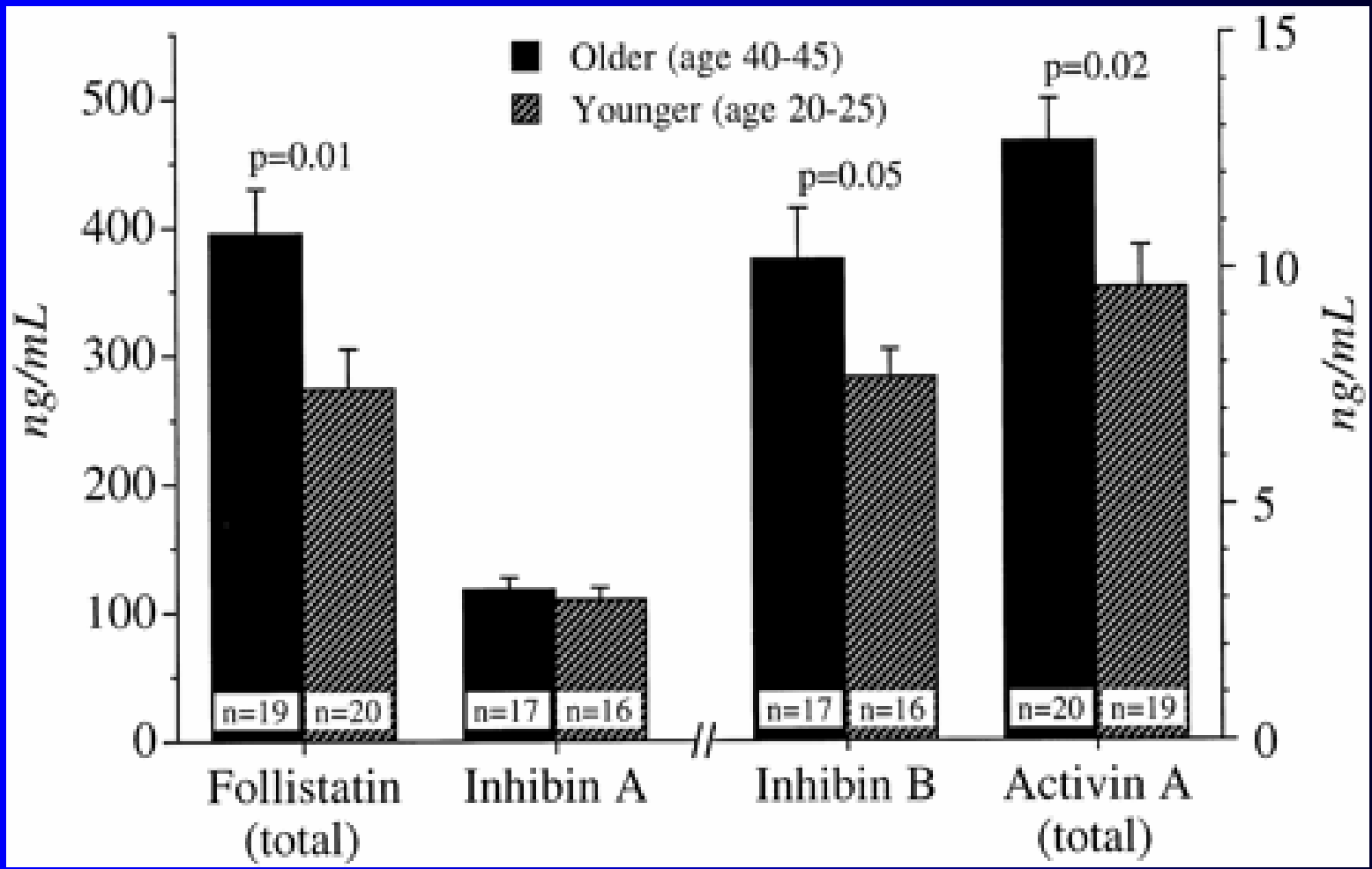
Changes

- The post-menopausal ovary (at 6-12 months of amenorrhea) is constituted mainly of hyperplasic connective tissue
- Some follicles will still be present and will disappear progressively between 24 and 48 months of amenorrhea



Mean follicular fluid concentrations for older subjects (40-45) and younger control (20-25)

From Klein et al. JCE 85, 4518-25,2000



Older subjects had significantly higher concentrations of total follistatin and activin A

No significant difference in concentrations of Inhibin A and B

From Klein et al. JCE 85, 4518-25,2000

Genetic factors?

- In contrast to the timing of onset of the menstrual cycle for which a considerable genetic influence has been shown data are not so clear for menopause.
- Attempts to relate menopause with different behavioural, reproductive and anthropometrical factors failed to show a consistent and replicable influence.
- Only smoking advances menopause of ~1.5-2 years

Genetic factors? II

- «Genes control the cessation of a woman's reproductive life: a twin study of hysterectomy and age at menopause»
  - classical twin study
  - 628 twin pairs
  - h2 = 63%

Snider H., MacGregor J., Spector T.D.
J Reprod Endocrinol Metab 1998

Factors known to modify the age of menopause

- Smoking (early onset)
- Ethnic origin and climate (early)
- Malnutrition (early)
- Hysterectomy (early)
- Fibroids ? (late)
- Alcohol (late)
- Obesity (late)

Factors known not to modify the age of menopause

- Age at puberty
- Oral contraception
- Ovarian stimulation
- Number of pregnancies
- Age at last pregnancy
- Lifestyle
- Height
- Weight

What happens at menopause ?

- In post-menopausal women estrogen levels are down to one tenth than their level during reproductive years
- Progesterone is nearly absent
- The small amounts of circulating hormones are produced not by the ovaries but by the adrenal glands and the fat cells

Target organs

- Bone
- Cardiovascular system
- Breast
- Uterus
- Ovary
- And muscle, skin, brain, etc.

Symptoms of menopause

- Absence of period
- Hot flashes
- Night sweats
- Sleeplessness
- Vaginal dryness
- Mood changes
- Skin and hair modifications
- Fatigue

HRT today
Still an option?

- Short and long term treatments
- Different indications and possibly different risks

Steroid hormones effects on cells

They can have different effects in different tissues

Estrogens are extra and intra cellular messengers and stimulate cell growth

In general they have a proliferative effect

Progesterone has a trophic effect

Progestins have mostly an atrophic effect on the endometrium

Hormones used for HRT

Estradiol

(17 β estradiol, estrogen valerate)

oral, transdermal, vaginally,i.m.

Conjugated estrogens

(50% estrone sulfate, 23% equiline)

oral, vaginal

Estriol

oral, vaginal

Hormones used for HRT

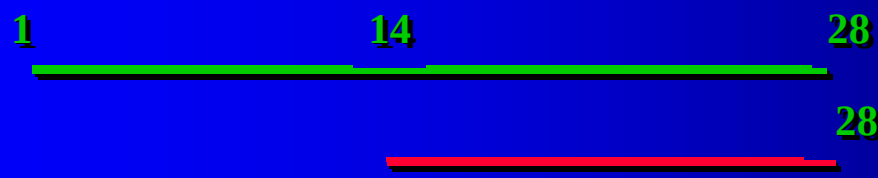
- Natural progesterone
- Progestins derived from progesterone
  - Acetate of medroxiprogesterone
  - Medrogestone,
  - Cyproteron acetate
  - Dihydrogesterone
- Progestins derived from nortestosterone
  - Norethisterone
  - Norgestrel, desogestrel, levonorgestrel, desogen, dienogest

Possible therapeutic schemes

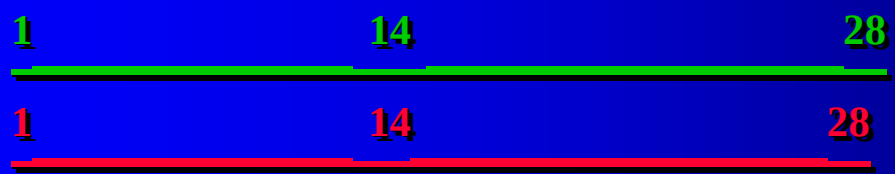
Estrogens only

Gestogens as cyclic monotherapy

Cyclic combined HRT



Continuous combined HRT



Epidemiology of HRT

- About 8 million women in the USA take estrogen alone and about 6 million are on the combined hormone regimen
- 45% of US women born between 1897 and 1950 used HRT for at least one month and 20% for 5 or more years

HRT effects on total circulating levels

- Hormone replacement therapy (HRT) only doubles the estrogen and progesterone levels of a post-menopausal woman thus by no means it restores the previous hormone environment of that woman or is capable of restoring any ovarian activity

The WHI study

- Aim of the study was to define risks and benefits of strategies that could reduce the incidence of heart disease, breast and colon cancer and fractures in post-menopausal women

The WHI study (2)

- 161 809 women aged between 50 and 79 years old were enrolled between 1993 and 1998 for a set of clinical studies on low-fat dietary patterns, Calcium and Vit D supplementation, 2 trials of post-menopausal hormone use and an observational study at 40 USA clinical centres

The WHI study (3)

- Type of studied HRT
  - Continuous combined HRT
  - Conjugated equine estrogens administered orally
  - Type of study
    - Double blind

WHI report : JAMA 7-17-2002 (1)

- 16 608 women with no history of hysterectomy had been enrolled for a randomised trial on continuous hormonal replacement treatment with equine estrogens and acetate of medroxiprogesterone
- The trial was stopped early because evidence of health risks exceeding health benefits over an average follow-up of 5.2 years

WHI report : JAMA 7-17-2002 (2)

The arm of the study on combined HRT was stopped after 5,2 years instead of 8 as intermediate monitoring of results showed that the risks outweighted the benefits

WHI report : JAMA 7-17-2002 (3)

Risk included small but significant increase in	Benefits included lower risk for
breast cancer	hip fractures
coronary heart disease	colon cancer
stroke	
blood clots	

NHI alert
3 /3/ 2004

- WHI completely stopped
- No benefits for the cardiovascular system

Heart disease risk

- The risk was 29% higher for the group taking combined HRT than the group on placebo
- The annual increased risk for an individual women was still relatively small
- In 1 year 37 heart disease events per 10.000 women were reported in the combined HRT protocol versus 30 in the placebo group

Breast cancer risk

- Risk was 26% higher in the treated group
- On average in one year 8 additional cases were observed in this group
- The increase was apparent after 4 years and the risk appeared to be cumulative

Stroke and blood clots risk

- 41% of increased risk for the group on HRT
- On average 29 cases per 10000 women vs. 20 cases
- The risk appeared in the 2nd year of treatment
- 2 fold greater rates of blood clots than the group on placebo
- On average 34 cases per 10000 women vs. 16 cases

Benefits shown by the combined HRT study –WHI

- Colon cancer
  - Reduction of 37% in the HRT group
  - On average 10 cases per 10000 women vs 16 cases in the placebo group
  - Benefit appeared after 3 years of use and became more significant with time

Benefits shown by the combined HRT study –WHI

- **Bone fractures**
  - **First study to show a decreased risk of vertebral and other osteoporotic fractures**
  - **24% reduction in total fractures and 34% reduction in hip fractures**
  - **10 vs. 15 cases (5 fewer cases per 10000 per year)**

Uterine cancer and HRT

- Prolonged exposure of the uterus to estrogens in the absence of progesterone increases the risk of endometrial cancer
- Progesterone or progestins must be used for at least 10 days to provide protection statistically

Ovarian cancer and HRT

- One recent study suggested that combined HRT do not increase the risk if Progesterone is used at least for 15 days a month
- Estrogens increases the risk of ovarian cancer and the risk increase with time of use (less or more than 20 y of treatment)

Osteoporosis and HRT

- HRT reduces of 30% the risk of hip fractures and 50% those of vertebrae
- One of the women over 80 will suffer of fractures
- A protective effect seems to exist and is time dependent (less and over 10 y)
- The time of treatment seems also to play a role

Alzheimer and HRT

- JAMA Nov. 2002
- 41% reduction in risk of AD (26 cases out of 1066 women who had used HRT vs 58 cases out of 800 non users)
- Women who had used HRT for 10 or more years has a risk comparable with the risk observed in men

Other substances used for relief of menopausal symptoms

Phyto – hormones

Black cohosh (cimifuga racemosa), lignins (flaxseeds), coumestans (sunflower seeds, red clover), isoflavones (soya), yam (extracts)

Androgens

Dehydroepiandrosterone

Testosterone

Other substances used for relief of menopausal symptoms

(Selective estrogen receptors modulators)

Raloxifene

SSRI and NRI

SERM

Modulators of the serotonin levels and 5-HT 2a receptors

Fluoxitine

Tibolone

(C19, derived from Norethisterone)
capable of interacting with estrogen, progestin and androgen receptors

- Hot flashes
- Sweating
- Dizziness
- Headaches
- Vaginal dryness
- Dyspareunia
- Decreases FSH
- Increases libido

Tibolone II

- No estrogenic activity on endometrium ??
- 12% of cases irregular bleeding (unexplained)
- Endometrium has showed to be atrophic at US and biopsy
- No impact on fibroids
- Can be associated to LHRH analogues to limit hypoestrogenic symptoms

Tibolone III

- **Effective on bone**
- **Reduces by 50% bone remodelling**

  but increases thromboembolic events (Thebes study data presented in Buenos Aires 2005)
- **less effects on breast**

  Until the One million women study (Lancet 2003) showed that this was not the case
- **Has an inotropic effect on heart and no impact on blood pressure**

Alternatives to hormone replacement therapy Osteoporosis

Adequate calcium and vitamin D intake (1000 to 1500 and exercise

<u>If at risk:</u>

Livial ??

recent results showed that as it increases bone density it increases also thromboembolic risk in older women (LIFT study) and that it could cause endometrial cancer (THEBES study)

Evista ??

important vasomotor side effects

Fosamax ??

Mandibular osteodistrophy

Raloxifene

- Derived from tamoxifene and mainly used for prevention of breast cancer recurrency
- Effects: agonists or antagonists on different tissues
- Used essentially for prevention and treatment of osteoporosis
- Effects also on the vascular system and metabolism
- Ongoing studies (Ruth, More)

Biphosphonates

- They decrease osteoclasts activity
- They are fixed by the bone
- Very little absorption
- Some side effects
- The effect last on bone up to one year after end of treatment

Alternatives to hormone replacement therapy
General advise

- Don’t smoke
- Eat a healthy diet
- Maintain a healthy weight
- Get adequate exercise
- Reduce stress

Alternatives to hormone replacement therapy
Hot flashes

- Lifestyle changes
- Soy foods
- Antidepressants (Effexor, Prozac, Paxil)
- Hypotensive drugs (Catapresan)

Alternatives to hormone replacement therapy Vaginal dryness

- Vaginal lubricants
- Vaginal estrogen products
  (creams, gels, ovules, vaginal ring)

Alternatives to hormone replacement therapy
Heart disease

- Control and maintain low cholesterol levels
- Control and maintain low blood pressure levels

Questions left open

- Will low doses of estrogens and progestin have lower risks?
- Do other types of estrogens and progestins or other ways of administering them have different risks?
- Which place for physiological HRT?
- What is the best method to stop taking estrogens and progestins

Conclusions

- More research is needed and welcomed
- A standard, perfect and safe dose for all women probably does not exist
- The best dose is the lowest capable of treating the symptoms in each patient
- Genetic and personal risks must be carefully evaluated