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 ménos (month) and pausis (pause)***

Perimenopause

- The term defines the period that preceeds (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?

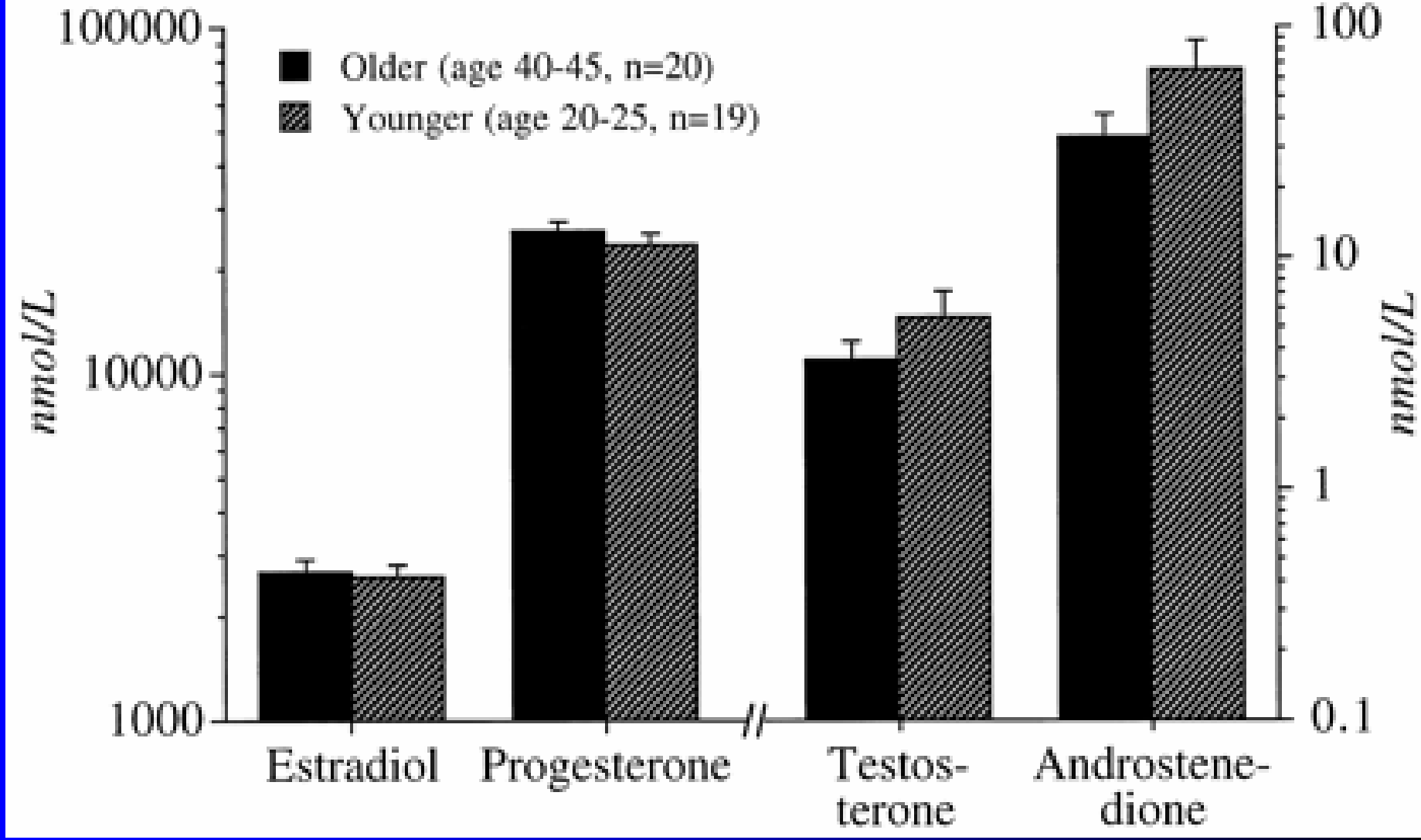
- Endocrine mechanisms
- Ovarian reserve
- Oocyte quality
- Implantation

Changes

- **Already 10 years before menopause slight changes in menstrual cyclicity 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 coincides with a phase of accelerated follicle depletion.

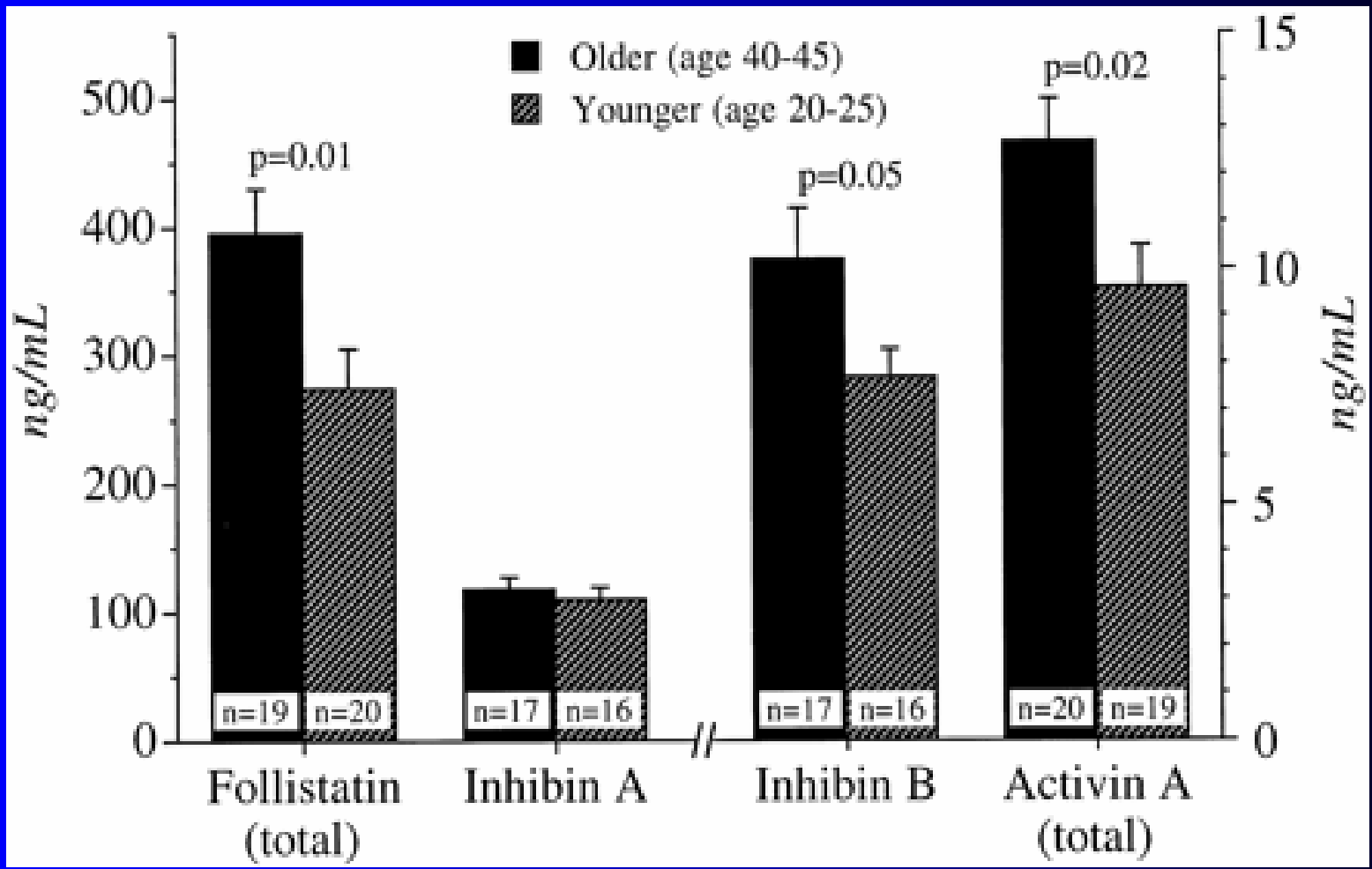
Changes

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



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 anthropometric 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 women'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 (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 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?

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% sulfate d'estrone, 23% equiline)

oral, vaginal

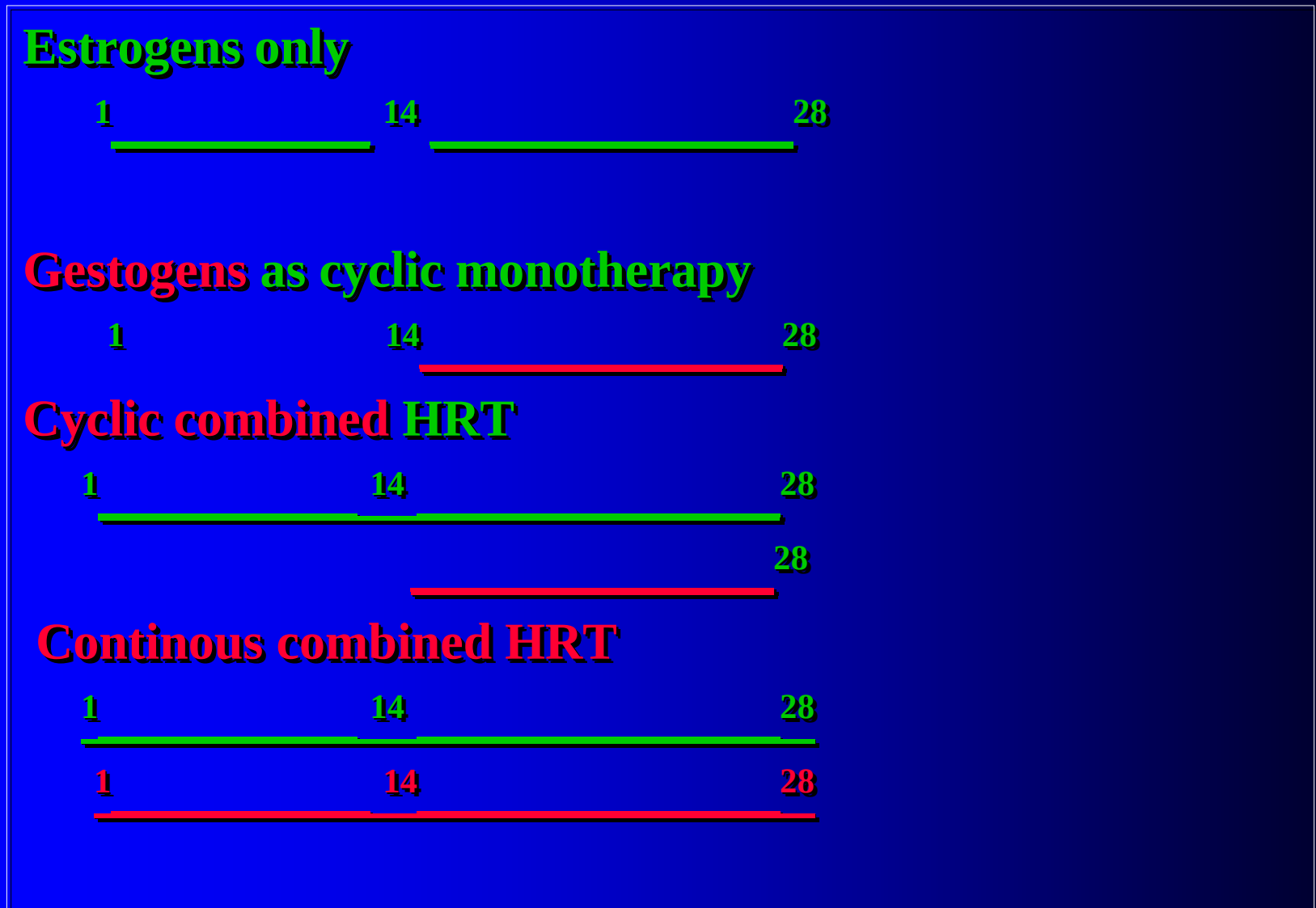
Estriol

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



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

Other substances used for relief of menopausal symptoms

Tibolone (C19, derived from Norethisteron)

syntetic analog of steroids capable of interacting with estrogen, progestin and androgen receptors

Raloxifene

Selective estrogen receptors modulator (SERM)

Phyto –estrogens

Fosamax

Androgens

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 centers

The WHI study (3)

- **Type of studied HRT**
  - **Continuos 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 continous hormonal replacement treatment with equine estrogens and acetate of medroxiprogesterone

- The trial was stopped early because evidence of health risks exceding 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 woman 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 apperead 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 P is used at least for 15 days a month
- Estrogens increase 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 woman 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

Tibolone

- Effective on:
- Hot flashes
- Sweating
- Dizziness
- Headaches
- Vaginal dryness
- Dyspaurenia
- 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 to limit hypoestrogenic symptoms

Tibolone III

- **Effective on bone**
- **Reduces by 50% bone remodelling**
- **Seems to have less effects on breast**
- **Inotropic effect on heart and no impact on blood pressure**

Raloxifene

- Derived from tamoxifen and mainly used for prevention of breast cancer recurrence
- 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 effects last on bone up to one y 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 lubrificants
- Vaginal estrogen products
  (creams, gels, ovules, vaginal ring)

Alternatives to hormone replacement therapy
Osteoporosis

Adequate calcium and vitamin D intake and exercise

If at risk: Livial, Evista and Fosamax

Alternatives to hormone replacement therapy
Heart disease

- Control and mantain low cholesterol levels
- Control and mantain 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?
- 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