The menopause

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What is menopause ?

- The permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy, or radiation. Natural menopause is recognized after 12 consecutive months without menstrual periods that are not associated with a physiologic or pathologic cause.
- The loss of ovarian activity.
- The end of reproductive capacity.
- The transition from childbearing years to non-childbearing years.

- *The term derives from the greek words ménos (month) and pausis (pause).*

Perimenopause

- The term defines the period immediately prior to menopause (when the biological and clinical features of approaching menopause begin) and the first year after menopause.
- Is characterized by progressive decrease in ovarian function and the appearance of the clinical and biological signs associated to this event.
- Can last several years.

Epidemiology of menopause

- Mean age of menopause varies according to studies:
  - Massachusetts Women's Health Study : 51.3 years
  - Mostly between 48 and 52 years
- 90% of women are menopaused between 45 and 55 years of age.
- Duration of postmenopause: life expectancy at birth (2010) is 30.6 years after the age of 50 for more developed countries, 19.6 years for less developed countries, and 8.4 years for least developed countries (UN Population Division, 1998).

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.
- 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.
- Small amounts of estrogens, mainly produced by the adrenal glands and the fat cells.

Target organs

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

Symptoms of menopause

- Absence of menstrual 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
- Possible alternative treatments

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
  - Cyproterone acetate
  - Dihydrogesterone
- Progestins derived from nortestosterone
  - Norethisterone
  - Norgestrel, desogestrel, levonorgestrel, desogen, dienogest

Possible therapeutic schemes

Estrogens only

1 — 14 — 28

Gestogens as cyclic monotherapy

1 — 14 — 28

Cyclic combined HRT

1 — 14 — 28

28

Continuous combined HRT

1 — 14 — 28

1 — 14 — 28

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 vitamine 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
  - 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 randomized 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 outweighed the benefits

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

Risk included small but significant increase in:

- breast cancer
- coronary heart disease
- stroke
- blood clots

Benefits included lower risk for:

- hip fractures
- colon cancer

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).

Other substances used for relief of menopausal symptoms

Phytohormones

black cohosh-cimifuga racaemosa, lignins

(flaxseeds), coumestans (sunflower seeds, red clover),

isoflavones (soya), yam (extracts)

Androgens

Dehydroepiandrosterone

Testosterone

Other substances used for relief of menopausal symptoms

SERM

Selective estrogen receptors modulators

Raloxifene

SSRI and NRI

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
- 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 GnRH analogues to limit hypoestrogenic symptoms.

Tibolone III

- Effective on bone.
- Reduces by 50% bone remodeling

  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.

Raloxifene

- Derived from tamoxifene and mainly used for prevention of breast cancer recurrences.
- Effects: agonists or antagonists on different tissues.
- Used essentially for prevention and treatment of osteoporosis.
- Effects also on the vascular system and metabolism.

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)

Biphosphonates

- They decrease osteoclast activity.
- They are fixed by the bone.
- Very little absorption.
- Some side effects.

Alternatives to hormone replacement therapy
Vaginal dryness

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

Questions left open

- Will low doses of estrogens and progestins 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

New promising trends

- New low and ultra-low-dose oral preparations (containing 0.3 mg conjugated equine estrogens and 0.5 mg estradiol respectively).
- A 14 mg estrogen transdermal system.
- New progestogens.
- New androgen patch.
- New SERM in association with conjugated equine estrogens.