

EDITORIAL

What about breast cancer and cardiovascular disease risks with the best treatments during the climacterium and beyond

MANUEL NEVES-E-CASTRO

Honorary Founding President, Portuguese Menopause Society, and Honorary Member and past Vice-President, European Menopause and Andropause Society, Lisbon, Portugal

There is a general tendency to consider that sex steroid hormones are the only instruments with which to treat women when they enter the climacteric phase of their lives. Both women and physicians share this assumption. Otherwise the ongoing discussions that have exploded all over the world would not have been centered only in the risk–benefit assessment of hormonal treatments.

The climacteric is a complex phase of a woman's life, being the transition from the reproductive to the non-reproductive years. There are many symptoms that may interfere with women's quality of life during this time, derived either from hormonal imbalances and deficiencies or from factors arising from the microsocial or macrosocial environments that surround them.

The climacteric, due to hormonal causes and aging, is also a time for the onset of several risk factors for diseases that may be manifested later in life. Cardiovascular diseases (CVD), osteoporosis and degenerative diseases of the central nervous system (CNS), to name only the major ones, may have an impact on the duration and quality of life.

There are abundant epidemiological studies that confirm the increased incidence of such diseases, as well as many others, in untreated women, and give benefit–risk analyses of the hormonal treatments to which women receiving medication have been submitted. However, little attention is paid to other pharmacological interventions (non-hormonal) and strategies that have been shown to be important for the prevention of such diseases and to maintain or improve health.

What has been learned from the major observational studies and clinical trials?

It appears that the **first lesson**, previously unsuspected, is that systematically administered synthetic progestogens may in part suppress some of the beneficial effects of estrogens and may also slightly increase the risk of breast cancer after treatments with duration greater than 5 years. This being the case, it was also found that not all progestogens are alike in terms of their side-effects. The fact that, as a class, these steroids display progestogenic effects in some targets does not mean that they are identical to natural progesterone. In this respect it seems that retoprogesterone and 19-norpregnanes better approach the profile of progesterone. Therefore, it is regrettable that most publications refer to all progestogens as only one class of molecule, when they should instead indicate which particular progestogen was used in an investigation.

The **second lesson** is the most surprising information that estrogens, when given alone to hysterectomized women, did not appear to minimally affect the risk for breast cancer compared with controls. Again, not all estrogens are alike, although the differences between conjugated equine estrogens and estradiol, or its esters, are not so marked as is the case with progestogens.

Third, the metabolic effects of estrogens and progestogens, as a whole, can differ depending on the route of administration, i.e., oral versus parenteral, and on the combination of both, in a sequential regimen or in continuous combined administration. The parenteral routes that have been used are the transcutaneous (patches, gels), the subcutaneous

(implants), the vaginal (medicated rings and suppositories) and the intrauterine (progestogen-loaded intrauterine devices).

The **fourth lesson** is that hormonal treatments are the first choice for vasomotor symptom relief as long as they are needed (on and off assessment). They should not be used for the secondary prevention of CVD, when atheroma plaques are already present. Conversely, they may protect from CVD if started early during the transition into the postmenopause. Hormonal treatments are preventive of osteopenia and osteoporosis at any stage in life, if there are no contraindications, and have additive effects with non-hormonal medications such as bisphosphonates. Estrogens may prevent degenerative lesions of the CNS since, so far, they seem to be the only available drugs with nerve growth effects.

How do the hormonal treatments compare with other non-hormonal medications and strategies?

Any comparison, to be feasible and acceptable, must be based on the level of evidence and on results. Then, one of the best indicators of the efficacy of a treatment is the so-called a 'number needed to treat' (NNT), i.e. how many persons must be submitted to a treatment before one individual shows the benefit of the therapy. This figure can be calculated from the results of any well-performed study, but unfortunately is often omitted.

The following are some of the possibilities available.

Exercise

There is good evidence that aerobic exercise and weight-bearing exercises are beneficial to prevent not only CVD and osteoporosis, but also breast cancer.

Nutrition

It is already known that low-fat diets are good, as is high consumption of vegetables and fruits, soy, almonds and nuts, carbohydrates, fish, milk, etc. Recently a 'polymeal' containing dark chocolate and garlic among its ingredients was proposed with claims of 75% success in the prevention of CVD.

Medications

- (1) Statins may prevent CVD, and have effects on bone and CNS. There are strong suggestions that they may also prevent breast cancer.
- (2) Calcium may prevent osteoporosis and colon cancer.
- (3) Vitamin D may prevent osteoporosis and colon cancer.
- (4) Non-steroidal anti-inflammatory drugs may prevent CVD, breast cancer and colon cancer,

but, after long treatments, may increase myocardial infarction, pancreatic cancer (?) and gastric ulcers.

- (5) The 'polypill', in view of the above, a mixture of several drugs, has been proposed with the claim that it might prevent or reduce CVD by 80%.

What are the best treatments?

In general terms, *the best treatment is the one that is wisely indicated, if not contraindicated, after balancing benefits and risks of all strategies and interventions, hormonal or not.* It must be aimed at specific objectives and targets that will be monitored at regular intervals to determine its efficacy and to estimate the occurrence of any side-effects, a condition that will determine its duration. *The patient's needs and preferences are decisive, based on the doctor's advice.* Let it not be forgotten that although many treatments are available, *they are nevertheless not indispensable.* Doctors have the duty to give the best, unbiased information to their patients so that they may make the right choices and then be compliant. *The woman is the decision-maker, if the doctor sees no contraindication.* Thus, *the best treatment is what she has chosen.*

Are there risks?

Any treatment or no treatment at all (e.g. placebos) has benefits and risks. What is important is to let the woman know how any risk compares with other preventable risks that she faces every day, without quantifying them, that are several orders of magnitude greater than those attributed to hormonal treatments. It is crucial that information be given about the difference between relative risks and absolute risks, since the former are the major cause of misinformation and alarmism, being the favorite of the media.

What are the best recommendations of the climacteric woman's doctor?

- (1) Understand what is happening to the body during the climacteric and beyond.
- (2) Mental occupation.
- (3) Physical exercise.
- (4) Proper nutrition (moderate consumption of red wine, and abundant fish, vegetables, fruits, soy, milk, garlic, chocolate, etc.).
- (5) Keep the body mass index within normal limits.
- (6) Keep a normal waist-to-hip ratio.
- (7) Refrain from smoking.
- (8) Keep a normal blood pressure.
- (9) Keep the blood lipids within normal values (statins?).
- (10) Examine the breasts (palpation, inspection, mammography).

- (11) For vasomotor symptoms and night sweats take a sequential estrogen plus progestogen medication, the most inert being an estrogen patch plus oral or vaginal micronized progesterone (alternatively, a progestogen-loaded intrauterine device). If hysterectomized, take only estrogen (no need for progestogen).
- (12) If libido is still down, add testosterone or switch to tibolone.
- (13) If breasts are tender and dense, adjust dosages or use tibolone instead of estrogen (plus progestogen).
- (14) Use vaginal estrogens if vagina is dry and if there is dyspareunia.
- (15) If osteoporotic add bisphosphonates or tibolone.
- (16) Check stools for occult blood and do the first colonoscopy at age 50 and thereafter at 5-year intervals.
- (17) Last but not least, enjoy life and help other women to do what you are doing.

Recommended reading

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