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Is there a menopausal medicine? The past, the present and the future☆

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Abstract

The menopause is not a disease. However it is the onset of risks for the diseases that are more prevalent after the fifth decade of a woman's life. These are due both to the natural process of ageing and to the lack of the protective effect of estrogens that are then secreted in much lower amounts. Estrogen treatments after the menopause should not be considered as replacements, since hypoestrogenism is physiologic after age 50. They are only treatments with sex hormones, with specific indications, as there are also recommended treatments without hormones. This clarification of concepts is essential in order to emphasize that hormonal treatments after the menopause are not obligatory and may have good alternatives too. Thus, the ongoing discussion should not be about the pros and cons of long-term hormonal treatments but, instead, about what is best for the preservation of health, the prevention of diseases and the maintenance of a good quality of a woman's life after age 50. © 2002 Published by Elsevier Science Ireland Ltd.

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1. Historical background

Treatments with organs and their extracts were already reported in ancient times in Egypt, Greece and Rome. It took several centuries until in 1986 three German groups claimed that treatments with 'ovarian powders' relieved symptoms related to the menopause.

What we all know today about estrogens is due to some fundamental concepts and observations made during the 19th and early 20th centuries. The notion of an 'internal secretion' was first suggested by Theophile de Bordeu in 1755 but only in 1855 further developed by Claude Bernard, in France. Baylis, Starling and William Hardy coined the name 'hormones'. Stockard and Papanicolaou described in 1917 the estrogenic effects in the vagina, and in 1924 Allen and Doisy found estrogenic effects in the uterus of rodents.

These observations contributed to the purification of hormone extracts from the ovaries, with fat solvents, by Parkes and Bellerby in 1926, known as 'estrin'. Estrone was isolated in 1929 by Butenandt, in pure form, from the urine of pregnant women. Marian, in the UK, isolated estriol also from the urine of pregnant women. Only in 1940 17β-estradiol was isolated from the urine of pregnant women, too, and from the placenta.

The first report of a therapeutic use of estro-

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gens in the menopause, for hot flashes, sweating, irritability and libido is certainly the one of Geist and Spillman [1] in 1932.

An enormous contribution to the hormonal treatments for menopausal women was done by two pharmaceutical companies: Schering, in Germany, and Organon, in the Netherlands. The first pure estrogenic medicines available in the market were 'Progynon' from Schering, 'Ovestin' from Organon, 'Premarin' from Wyeth. Meanwhile, other than pure injectable progesterone, synthetic progestagens were developed and marketed by Schering ('Primolut') and Parke Davies ('Norlutin'). This was what was needed to open a new era in therapy, specially after Fuller Albright described in 1940 the menopausal osteoporosis due to hypoestrogenism, and Robert Wilson launched in 1966 a campaign claiming that women could be 'feminine for ever' if they were medicated with estrogens.

However, the first relevant scientific contributions to this field were made by three pioneers: Robert B. Greenblatt (USA), Wulf H. Utian (South Africa, and later in the USA) and Pieter van Keep (The Netherlands). The first one developed an enormous experience in the treatment with estradiol and testosterone subcutaneous implants; the second, started the first menopause clinics and the third founded the International Menopause Society and organized the first Congresses on the Menopause.

This was the beginning of many studies in the field of the menopause. There was great enthusiasm but still little knowledge about doses, combination treatments, diagnosis of risk factors, etc. Quality of life was no doubt improved and, thus, women did not want to stop hormonal medications. Therefore, treatments were continued non stop, sometimes with even higher doses and not associated with progestagens. And, as time went on; the first side effects started being reported, as it was to be expected. Could estrogens cause endometrial and breast cancer? Could they cause vascular diseases? These were some of the questions that the past has sent for the present to answer. This is where we are now, in the present.

2. Today's problems

Before going any further, I think that it is relevant to ask some other questions, not about the good or the bad effects of the treatments with the so called female hormones but, instead, about the objectives that must guide medical practice and the characteristics of the subjects to whom it is addressed.

As physicians, our main goal is to do our best to preserve and improve health, to prevent diseases and to diagnose and treat them well. Therefore, there are at least three major concepts: health maintenance, disease prevention, diagnosis and treatment of diseases.

The WHO defines Health as 'a condition of physical, mental and social wellbeing and not only the absence of disease'. Thus; the first step is to assess Health, a very complex task much more difficult than the diagnosis of disease.

The subject of our attention is a menopausal mid-aged woman. As a menopausal woman, she is hypoestrogenic, and may suffer, at various levels, from its consequences. But, as a mid-aged woman, she will suffer, too, from the process of natural ageing, both from a biological and psychologic prespective. This is our task to conjugate and equate the problems, to transform complex equations into simpler questions, and to find the answers that best fit them.

What do we know today about postmenopausal women?

What do we know about their health promotion strategies, disease prevention and treatments with or without female steroid hormones?

There is no doubt that the lifetime risk of death, for a 50-year-old postmenopausal woman, is 30% for heart disease, 3% for breast cancer and 3% for hip fracture complications [2].The mortality due to heart disease is also much higher than the mortality due to breast cancer. However, the mortality among women who use postmenopausal hormones is lower than among nonusers [3]. Therefore, the primary and secondary prevention of heart diseases is extremely important. The prevention of osteoporosis comes next. And it goes without saying that anything that contributes to a better quality of life is equally important.

Can this be achieved with or without hormonal treatments, or with a combination of both? For how long? And how does one know if such interventions are indeed being efficacious? What is the result of a benefit/risk analysis, taking into consideration breast cancer and cardiovascular events? These are the problems of the present time that must be solved for the future.

I shall not refer to HRT or ERT (replacement therapies) because, after the menopause one is not replacing any hormones. One can replace estrogens in a surgical or premature menopause, or in cases of gonadal agenesis, but not in the natural postmenopause when hypoestrogenism is physiologic. One replaces e.g. insulin in a type 1 diabetic, or cortisone in Addison's disease. In the natural postmenopause one may use hormonal *treatments*, just as nonhormonal medicines, *but not hormonal replacements*! This is not a question of semantics. It is, specially nowadays, a fundamental concept to emphasize that hormonal treatments are not necessarily obligatory in the postmenopause. They are excellent, if not contraindicated, either in the short or long term. And it is important that women understand and be reassured that there are many different and equally good ways to promote health and prevent diseases. The importance of a good nutrition, proper exercise and mental occupation are never sufficiently stressed by physicians and yet their consequences may far outweigh the role played by any remedy. The negative impact of smoking, of obesity or leanness, in terms of heart and bone health, are seldom discussed with those women who seek hormonal treatments.

Many clinical trials (prospective) and observational studies (retrospective) related to the improperly so called HRT's have been recently published, sometimes first in the lay than in the medical press. Their interpretation by less critical physicians and by the women themselves is open to serious mistakes. Most of the fixed protocols which are required in clinical trials do not necessarily reflect good clinical practice, an art of adjusting the right dose for a particular woman in order to avoid side-effects and yet achieve the treatment objectives. The selection of women for a clinical trial does not often reflect the general population that comes to a physician's office. Observational studies are more in line with what is done in clinical practice, since the structure of the hormones taken is not identical and the doses administered have been adapted to each individual; however, they may suffer from possible bias that may interfere with the validity of their conclusions. A major misinterpretation of these studies is the confusion of what is meant by an increased risk. An increased risk e.g. of 50% over a control group of women does not mean that in the treated group half of the women will suffer that side effect! This is a relative risk; not an absolute risk! It only means that there will be 50% more cases in the treated group than what was already expected in the control group. In the largest observational study [4] on HRT and breast cancer a 35–50% increased risk after 10–15 years of HRT signifies that it caused only 6–12 additional cases in 1000 women! Furthermore, a study done with a particular progestagen or estrogen, and only with a fixed dose, cannot be extrapolated to other molecules and regimens. As to the progestagens they can be either pregnane or estrane derivatives, without or with androgenic properties, etc. The pharmacokinetics and efficacy of different estrogens are not equivalent. Different estrogens may have different activities in different tissues; the potency and efficacy of a specific estrogen can vary from tissue to tissue; and there are differences among women with respect to estrogens in various tissues [5]. Estrogen receptor β inhibits estrogen receptor α in cells with both receptors; the cellular sensitivity to estradiol is reduced in cells with both receptors [6]. So, how is it possible to extrapolate data from one estrogen into another one, from one progestagen to another?

As to the breast cancer increased incidence under hormonal treatments, a major concern among women and physicians, it is estimated that only 1 in 397 women taking estrogens over 10 years would develop a breast cancer that would not ordinarily occurred if estrogen treatments were not used [7].

And 1 excess breast cancer case is likely to occur per 5–6 of first myocardial infarction or hip fracture that are prevented [8]. In a recent posthu-

mous article [9] Trudy Bush wrote that 'the evidence did not support the hypothesis that estrogen use increases the risk of breast cancer and that combined hormone therapy increases the risk more than estrogen only. Additional observational studies are unlikely to alter this conclusion'. A recent reanalysis of individual data from 52 epidemiological studies [10] concluded that 1/9 women who develop breast cancer may have an affected mother, sister or daughter, a risk factor to be kept in mind before the initiation of a long-term hormonal treatment in the postmenopause. And last, but not least, women who had breast cancer (clinically cured) and initiated an estrogen treatment had less recurrences and a longer survival than untreated controls [11].

The potential cardiovascular risks increased by estrogen/progestagen therapies have also been very much emphasized after the conclusions of the HERS trial. I do not think that these risks are realistic in our practice, as I have previously discussed [12]. The HERS trial authors are the first to recognize [13] that 'the discrepancy between the findings of HERS and the observational studies may also reflect important differences between the study populations and treatments' and also that 'for women who stopped taking HERS medication, the risk of primary CHD events was elevated in the 1st month after stopping use of the medication'. And again, they continue with these warnings: 'Perhaps postmenopausal hormone therapy is beneficial in women who have not yet developed coronary disease but not in women who already have it' and that 'the findings of HERS should not discourage the use of hormone replacement therapy in the primary prevention of cardiovascular diseases'. Later on, the American Heart Association issued a statement for Healthcare Professionals about HRT and Cardiovascular disease [14] where it is written that 'there are insufficient data to suggest that HRT should be initiated for the sole purpose of primary prevention on CVD'. Most surprisingly, in a foot note of the same statement, the authors seem to contradict themselves: 'the majority of data available to make clinical recommendations are based on standard doses of oral CEE/MPA. Evidence is insufficient to determine whether different preparations, routes of delivery, doses, or different progestins have a more favourable or adverse effect on clinical CVD end points'… In a recent publication [15] I wrote that 'recommendations such as these of the AHA, written as they are, may be less helpful than intended, both for clinicians and women'. Several well done studies, recently published [16], concluded that in postmenopausal women with stable angina, under treatment with estradiol/norethisterone acetate the number of ischemic events/24 h decreased by 0.82 events after treatment compared with an increase in the placebo group, of 0.94, a highly significant difference ($P = 0.006$)! And in the Nurse's Health Study [17] there is evidence that estrogens prevent cardiovascular diseases!

These are examples of the difficulties in the interpretation of many studies that show how limited are the possibilities to extrapolate them into clinical practice.

An important recommendation is not to read only the titles of those publications, or only the abstracts. The full paper should be critically read before one makes up his own mind. Confusions are often made between 'morbidity' and 'mortality', which are obviously very different. Many times those studies refer to 'woman/year', a concept subject to criticism. When one refers e.g. to 100 woman/years this could mean either 100 women treated during 12 months or 400 women treated during 3 months. Would the strength of a conclusion be the same in either case?

The benefits of estrogen treatments are quite evident for anyone who has a long experience in supporting postmenopausal women. We may or may not have a good tool for the primary prevention of cardiovascular diseases with a very small risk for breast cancer. We may increase bone mineral density, wether or not fractures are 'ipso facto' preventable. We may prevent colon cancer [18]. We may or may not prevent senile dementias. But what is quickly visible and felt, by the women themselves and by their attending physicians, is a remarkable improvement in mood and quality of life, by whatever mechanism, with or without the support of measurements of mental performance, with appropriate scales. This is more than enough to contemplate estrogen treat-

ments, after a proper evaluation of contraindications, for the length of time that is needed and acceptable on the basis of frequent reassessments. Let it be remembered that at the central nervous system estrogens act like neurotransmitters and are, so far, the only existing molecules with nerve growth activity.

Of course there are cases when the so called HRT is not possible [19] either because it is contraindicated, or is not wanted by women, or even because it may not be needed. Under these circumstances one must carefully evaluate risk factors or existing diseases (cardiovascular, cancer, bone, CNS).

There are nowadays many good nonhormonal medicines that can be used alone or in combination(or even in addition to hormonal treatments) like statins, bisphosphonates, thiazide diuretics, β-blockers, calcium-chanel blockers, ACE inhibitors, tranquilizers, psychotropics, Vitamin D derivatives, calcium, calcitonin, aspirin, etc. And I recall what I said before about the unquestionable merits of regular exercise, well balanced nutrition, stop smoking, mental occupation, etc. All the above have well proven beneficial effects both for symptom relief and for the primary and secondary prevention of the disease that are more prevalent after the menopause [20,21].

And worth considering, too, are some other modified estrogen receptor ligands, like SERM's, tibolone, or new estradiol conjugates (sulfamates), and newer and better progestagens that are also being developed (drosperinone).

3. The coming days

The future looks promising. The combination of hormonal and nonhormonal remedies is certainly a good strategy to augment the positive effects and to decrease side effects. Lower doses of hormones are being shown to be as effective as the present standard doses of estrogens. New delivery systems are expected to improve treatment continuation (compliance). Progestagen loaded intrauterine devices [22] can be inserted to protect the endometrium and avoid systemic administration of progestagens in association with estrogens. Nitroglycerin seems to be as efficacious as standard estrogen therapy in prevention of oophorectomy-induced bone loss, in women [23], in addition to its vascular effects. Phytoestrogens may eventually be useful. Testosterone is again being considered for some women. Dehidroepiandrosterone is still inconclusive.

But the important issue, after all, is not the hormonal treatment after the menopause. What is important is the best possible approach to preventive medicine in a mid-aged woman. This requires from the attending physician (gynaecologist, endocrinologist) the development of many talents as an empathic human being, capable of establishing a good raport, as an internist, who is able to interprete symptoms that are not necessarily related to his speciality and, no doubt, as a good well informed scientifically minded specialist.

This is why I do not think there is a menopausal medicine; there is only the Medicine of mid-aged women who reach the menopause. In his lectures Leon Speroff concludes that 'There is only one Medicine'. I go one step beyond and say that there are only two Medicines: the Good Medicine and the Bad Medicine. Was it not the case, then a gynaecologist would be only confined to the prescription of hormones or would have to be constantly referring the postmenopausal woman to many other different specialists. This referral will only be needed when he becomes aware that he has reached the natural limit of his competence in another area.

The therapeutic support during the climacterium is not confined only to drugs. It is not the menopause that is going to be treated. It is a woman, in a very special period of her life, with affective and hormonal imbalances, who needs to be supported and treated as a whole, that she is. It is essential to adopt a holistic vision of the middle aged woman and be concerned with all the aspects that define Health (WHO).

For a woman, the menopause is like an Alarm-Clock! An alarm given by Nature, as a reminder that she must stop and reflect about the next 30 years she may still live. An opportunity for a check-up. The time to set new goals and define strategies to fulfil them.

Sir William Osler once said that 'Science is an

art of probability, and Medicine is an art of uncertainty'. This is the challenge in our daily practice. This is why physicians should only give advice, whereas women are the ones who must make the decisions.

Let us not be totally dominated by the Evidence Based Medicine and let us allow some room for the Medicine Based Evidence.

Preventing a woman from the benefits of a *sound* postmenopausal hormone therapy, because of the fear of rare side effects, **does not seem to be satisfactory Medicine**… **Good clinical judgement must prevail!**

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