HORMONE REPLACEMENT THERAPY: IGNORANCE, MISCONCEPTIONS, FEARS

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The most important hormones in the ovary – estrogens and gestagens – are important not only for reproduction, i.e. to secure progeny. They are also important substances for the metabolism of the female organism in general. Taking into account the effects on the various organs and systems of the body, the classification as sexual hormones corresponds only with a partial effect.

Estrogen deficiency causes loss of bone substance, and after a sufficiently long period it ultimately leads to osteoporosis with all its complications. Estrogen deficiency has negative effects on vascular regulation and lipid metabolism, which results in a massive increase in the incidence of cardiovascular disease [1, 2]. Estrogens also have a variety of effects on the performance of the central nervous system; estrogen deficiency for a longer period of time impairs the cognitive performance and promotes the onset of dementia in old age [3–6]. These newer findings clearly show that a woman's ovary is an important endocrine organ, and that the loss of ovarian function in the climacterium can by no means be regarded as "natural". It is important that all women should be informed about the possible consequences of an estrogen deficiency over a period of 30 years or more. Genetically determined risks for diseases in old age, e.g. for osteoporosis, coronary heart disease or dementia, can be influenced by various measures; the onset of such diseases can be postponed to later age groups, as a result of which the term "compression of morbidity" has been coined. In this context, the hormones of the ovary and in particular the estrogens play a very significant role in the female body.

IGNORANCE OF BENEFITS

What we know today about the benefits of long-term hormone therapy in the postmenopause to avoid psychovegetative complaints and to prevent osteoporosis, coronary heart disease and reduced performance of the central nervous system would make the broadest possible application of hormone replacement appear sensible [7–9]. One of the reasons why treatment is not started or a started therapy is discontinued after a short time is the unfounded fear that the hormones could cause cancer (see below). Other reasons are fears that menstruation might recur or worries about weight gain. A particularly serious reason is the uncertainty caused by package inserts listing "contraindications" that are actually indications for hormone replacement (see below).

The level of knowledge about benefits and risks of hormone replacement therapy in Germany is entirely unsatisfactory – despite declarations to the contrary. In a survey conducted by the Demoscopic Institute Allensbach, Germany, in 1992 (sponsored by Schering

AG Berlin), more than 4000 women of different age groups were asked about the conditions for which they thought that good drugs were available (Fig. 1). The question concerning drugs for headaches or gastrointestinal disorders was generally answered positively. When asked whether there were any good drugs for the complaints associated with the menopause, two thirds of the women interviewed stated that this was not the case. Of those women interviewed who were actually suffering from menopause complaints at the time of the survey, three out of five women answered that they were not aware of any suitable drugs for this complex of symptoms. The answers concerning drugs against frailty of the bone in old age were even worse; thereby, the questions did not specifically refer to hormones. Only 13% of the women interviewed gave a positive answer, i.e. seven out of eight women consider osteoporosis in old age to be a matter of fate. These data scream for amends, whereby not only information by the medical professions but also activities by the media are required.

Recurrence of Menstruation

During the perimenopause, the estrogen concentrations in the blood drop sharply; in the postmenopause, the estradiol serum levels are around 10 pg/ml; they are the result of peripheral conversion of the adrenocortical androgens. In the postmenopause, the ovary is of no practical significance for these concentrations. If the level drops below the proliferation dose for the endometrium, usually at about 40–60 pg/ml of serum, amenorrhea sets in. Vice versa, estrogen replacement in the postmenopause should reach the above serum levels if possible, in order to guarantee bone and vessel protection; this means that there is also proliferation of the endometrium during the early postmenopause. In the long term, both continuous and cyclical estrogen therapy can lead to hyperplasia and thus to an increased risk of endometrial carcinoma [10, 11]. After only three months of estrogen monotherapy, hyperplasia of the endometrium is found in 10% of the treated women. Cyclical gestagen administration for a period of 13 days prevents the development of hyperplasia (Fig. 2) [12, 13]. This means that in the early postmenopause the woman must accept recurrence of the menstruation. As a general rule, the information that by accepting the menstruation she can reduce the risk of an endometrial carcinoma developing to far below that of an untreated woman will improve compliance.

In women in the later postmenopause, continuous combined estrogen-gestagen therapy can achieve amenorrhea immediately or in the medium term [14]. The continuous addition of gestagen results in atrophy of the endometrium despite estrogen stimulation (Fig. 3).

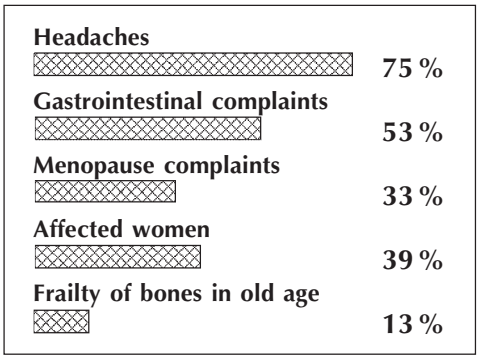

Figure 1. What conditions are good medications available for? (n = 4,355 women, Allensbach Survey 3216/1999)

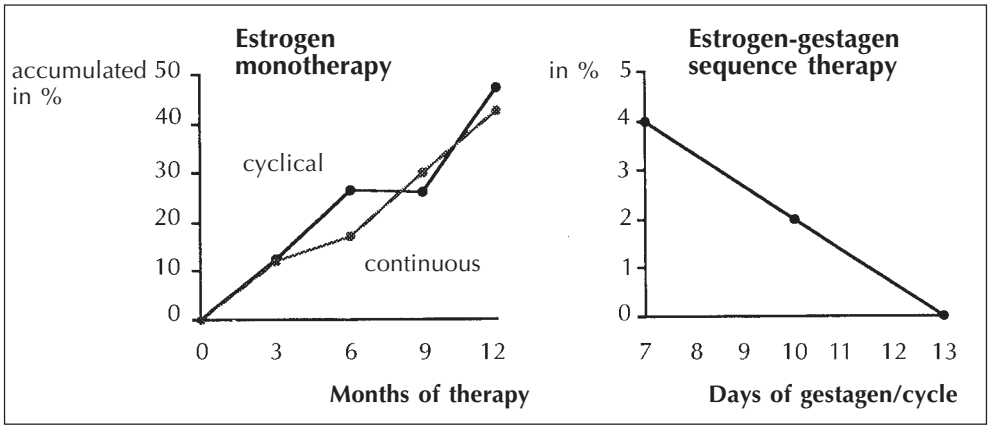

Figure 2. Left: Hyperplasia of the endometrium during cyclical or continuous estrogen therapy [10]. Right: Reduction of endometrium hyperplasia in relation to the duration of gestagen treatment [13]

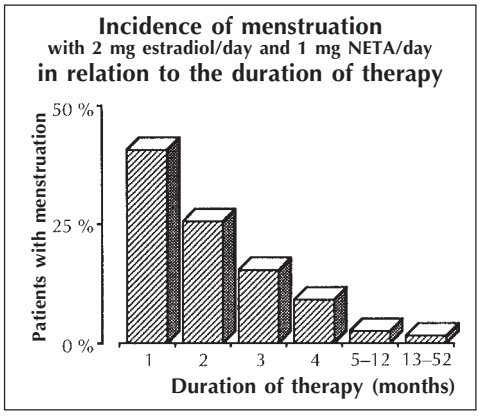

Figure 3. Incidence of menstruation during continuous combined estrogen-gestagen therapy in relation to the duration of treatment [14]

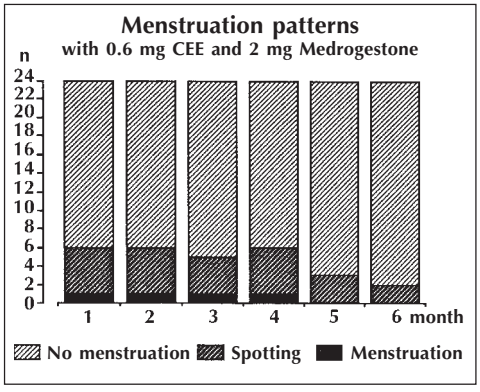

Figure 4. Menstruation pattern during 6 months of combined estrogen-gestagen therapy [15]

Own studies with a combined estrogen-gestagen therapy not yet authorized in Germany confirm these results [15]. After six months of this combined continuous therapy, only 2 out of 24 patients still had slight spotting, the remaining 22 patients were amenorrheal (Fig. 4).

Weight Problems

For women in the postmenopause and in old age, overweight is often a considerable problem. Once past the age of fifty, a marked weight increase is found in half of all women. As the supposed reason, the affected women often say: "I've gained a lot of weight since the menopause" or "I've gained a lot of weight since I've been on hormones". In the first case, it is assumed that the hormone deficiency induced an increase in weight, and in the latter case it is assumed that the hormone replacement leads to this effect. Any doctor can observe among his patients that older women have weight problems both with and without hormone

therapy. There is no association with estrogen-gestagen replacement. A great number of placebo-controlled studies with oral, transdermal and parenteral administration have excluded any such association [16–18]. Nor was any difference in the weight of the investigated women found when they were treated either cyclically or continuously with gestagen. One of these studies shows the weight condition of 50 women after hysterectomy and bilateral adnexectomy [19]. After three months without replacement, two different estrogens were administered; in between, there was a three-month placebo phase (Table 1). No differences in the weight were found.

Own data from transdermal estrogen therapy and oral gestagen therapy do not show any differences after 12 months of treatment either [20]. The weight gain/loss distribution ranges from –3.5 to +5 kg (Fig. 5). A weight gain in the postmenopause either with or without hormone therapy is an expression of changed lifestyle and habits.

The rehydration of skin and mucous must be regarded quite separately, however. The circulation is improved, wrinkles become smaller, and the general appearance is more youthful. The weight gain due to water retention rarely exceeds 1 kg. Occasionally, there may be a feeling of tension in the chest or mastodynia at the beginning of hormone replacement. However, these symptoms generally disappear again spontaneously within three months; in more serious cases, the estrogen dose should be reduced and the gestagen component modified, if necessary. A feeling of heaviness in the legs or aches in the lower leg are often interpreted as vascular reactions or misinterpreted as a thrombosis. Generally, these symptoms disappear quickly with a lower hormone dose and physical exercise. In patients who cannot cope with their weight problems and cannot be managed satisfactorily with dietetic measures, a short-term discontinuation of the hormone therapy may be necessary, which also demonstrates that the hormone withdrawal does not result in a weight reduction.

Table 1. Weight without hormone therapy and with two different estrogen regimes (E2V = 4 mg estradiol valerate/day, CEE = 5 mg conjugated equine estrogens) [19]

Controls	3 months	n = 50	66.28 kg
E_2V	3 months	n = 50	66.77 kg
E_2V	6 months	n = 50	65.88 kg
CEE	3 months	n = 50	66.75 kg
Placebo	3 months	n = 50	65.80 kg

Package Inserts and Contraindications

Once a woman has accepted that hormone therapy is good for her for therapeutic or preventive reasons after discussing the matter with her gynecologist, she may well become worried again after reading the (mis-)information in the package insert. In the best case, she will consult her gynecologist and he will inform her that the contraindications specified on the package insert are no longer in accordance with what we know today. More commonly, however, she will either not start the therapy or discontinue the therapy after a short time. Unfortunately, not only laypeople but even the attending general practitioners are not up to date on the facts. The condition after an apoplexia or high blood pressure is not a contraindication for hormone replacement therapy. In fact, women with these

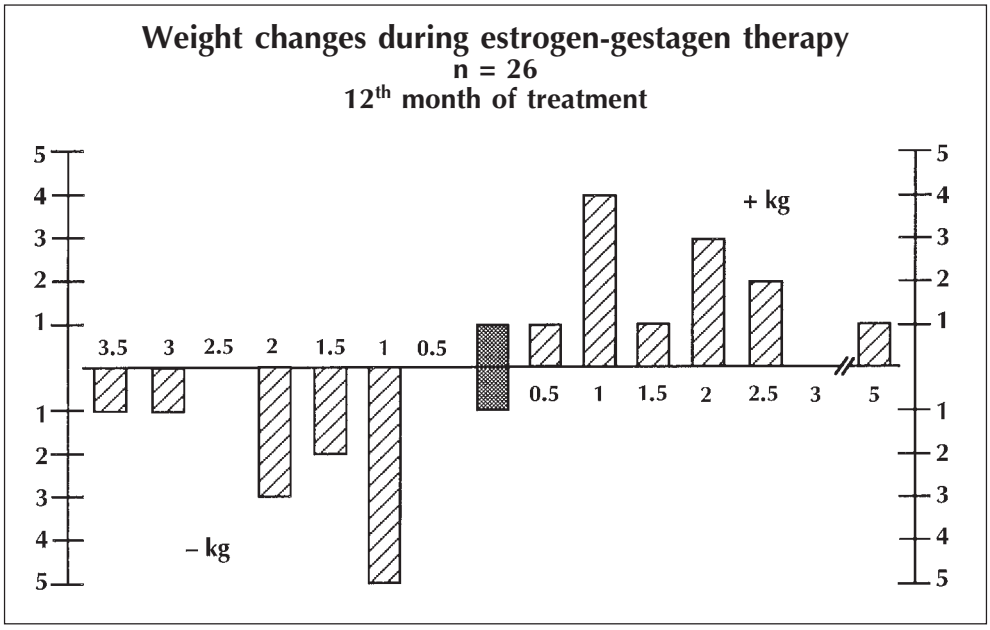

Figure 5. Weight changes after 12 months of estrogen-gestagen treatment (estradiol transdermal 0.05 mg/day, cyclical oral norethisterone acetate 1 mg) [20]

conditions often benefit quite considerably from such a therapy, i.e. these are true medical indications for replacement therapy (Table 2).

Other diseases listed as contraindications in the package insert cannot be considered as such any more nowadays, either (Table 3). In many cases, there is no need to do without replacement therapy after treatment for gynecological forms of cancer (Table 4). In fact, there are indications that the prognosis for endometrial carcinoma and ovarian carcinoma is improved by hormone therapy [21–24]. The Menopause Society of the German-speaking countries and its former president Prof. Dr. Lauritzen have long demanded that the package inserts for Germany be amended; so far, the recommendations by this Society have not been implemented, however. Once again, it is up to the medical professions and the media to provide the information.

Table 3. Not contraindicated

• Condition after thrombosis/embolism
• Diabetes mellitus
• Otosclerosis
• Sickle cell anemia

Table 2. Contraindications of yesterday – indications of today

• Hypertension
• Condition after stroke
• Hypercholesterolemia

Table 4. Hormone therapy after gynecological carcinomas

• Ovarian carcinoma
• Endometrial carcinoma
• Receptor-negative breast cancer

Hormones and Fear of Cancer

As mentioned above, the incidence of endometrial hyperplasia may be increased by estrogen monotherapy, as may the risk of endometrial carcinoma. The publication of these findings in the mid-seventies led to a general feeling of insecurity in the population worldwide. The knowledge that combined estrogen-gestagen treatment reduces the risk of cancer to far below that of an untreated women has not been disseminated accordingly [25–27]. In many parts of the German-speaking population, the fear of cancer being caused by hormones is still very widespread. Natural hormones, especially combined estrogen-gestagen preparations, do not have any confirmed effect on the development of cancer; in fact, they usually have a protective effect. There are indications that the prognosis for cancer diagnosed during hormone therapy is more favorable that if there is no hormone therapy [24, 28, 29]. Here, again, information by the medical professions and the media is an imperative (For details on hormones and cancer, see the chapter by Prof. Dr. Schneider).

Summary

The life expectation of a woman in Germany is now 81 years, i.e. every second woman born in 1920 is still alive. This means that the postmenopause now has a mean duration of thirty years. In addition to the life expectation itself, certain diseases of old age are also genetically programmed. These include cardiovascular diseases (myocardial infarction, stroke), osteoporosis and dementia. The onset of these diseases and the consequences for morbidity and mortality can be influenced favorably by lifestyle and habits (eating habits, physical exercise etc.). In terms of pharmacological prevention, the hormones and especially the estrogens are particularly important for women. Ignorance of the many benefits of hormone replacement or unjustified reservations and fears have so far prevented a more widespread application. It is not a question of "living to an old age", but rather one of enjoying old age with a good quality of life. It is a question of "compressing morbidity" in old age, i.e. keeping the time of illness prior to death as short as possible.

Therefore, everyone should join forces to inform about the positive effects of hormone replacement therapy [30]. In addition to further training for doctors, events for laypeople and patients (e.g. self-aid groups for osteoporosis patients), the whole range of media must also be employed. Without these measures, we will never succeed in reducing the problems and the costs of demographic ageing of the population in Central Europe. Not even a nursing care insurance is the solution.

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