HORMONE SUBSTITUTION BEFORE, DURING AND AFTER THE MENOPAUSE

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Climacteric is not a disease but a normal transitional period in female life. Some patients may have no complaints, however, if complaints occur, they may in certain cases be of such dimension that they can attain the character of an illness. A long-term hormone deficiency can even lead to genuine diseases. It is essential for us as physicians to convince women that menopause can be a chance for a new beginning, for new sources of freedom, the fulfilment of secret wishes, which had to be put back so far, and a gain of wisdom and calmness. All these possibilities, however, can only be experienced by those women, whose well-being is not restricted by pain, depression, lack of determination, and loss of physical and psychological activity. This is how estrogens can help fulfill wishes and support the realization of plans in a woman's third period of life. Women in their menopause thus have to make an important decision: Should they or should they not take hormones?

This decision sets the course for a woman's third period of life. When a climacteric woman takes estrogens/progestogens, she will suffer less cyclic disorders and will have less or no climacteric and uro-genital complaints. She might even spare herself curettages or an operation causing organ loss. Another important advantage is the fact that women taking hormones will generally undergo check-ups more regularly. This would give a better chance to detect and cure gynecologic disorders and cancer. On the other hand, a climacteric woman often suffers a number of worries and fears which her physician should be aware of. He should deal with these worries and fears and

Table 1. Worries and fears of climacteric women. N = 262, age group 48–65 years. University of Ulm, Dept. of Obstetrics and Gynecology, 1990

	Frequency in %
Fear of cancer	78
– Long lasting illness with pain and suffering	62
– operations	41
– osteoporosis	14
Worry about illness or death of partner	40
Not being able to get along in old age	39
Being permanently disabled, professional future	17
Financial and housing problems	27
Marriage problems, loss of libido, loss of attractiveness, not being a well accepted woman any more	32
Family problems	
– death of the parents	32*
– need of care of parents, adequate accomodation	17**
– worries about children	25***
Fear of menopause	28
– loss of libido	20
– gain of weight	63
– loss of well-being, joy of life	16
– loss of efficiency, energy	11
– loss of memory, concentration	4
Fear of or objections against hormones	44

* parents already dead in 21%;
** 3% of parents in need of care;
*** 8% have no children

possibly eliminate them (table 1). It has been shown statistically that a women in her late postmenopause or senium has a greater chance to enjoy her old-age in a better physical, mental, and psychological condition after application of a long-term estrogen-progestogen substitution. She will experience much less avoidable complaints, disturbances in well-being, and illness than a woman not taking hormones. Life expectation and life quality will most probably be improved.

Basis of medical recommendations

Statistics can only give information about a positive influence of estrogen intake on the incidence of disease in large population groups and do not give accurate and safe insight into a possible preventive effect of estrogens in a specific case. Therefore only predictions of a certain probability are possible for the individual case. This means, that the physician's recommendation for a hormonal substitution will accordingly only be based on assumptions and probabilities with varying degrees of certainty. Medical consultation will depend mainly on the kind and strength of the client's complaints, the results of the medical examination, and her wish for a specific treatment. The physician will, however, recommend strongly hormonal substitution in those cases, where anamnestic data, findings of medical examinations or risk factors exist pointing to the danger of a future illness which could be avoided by taking estrogens (table 2).

Table 2. Absolute indications for an estrogen-progestogen substitution in menopausal and postmenopausal women

- early spontaneous menopause (climacterium praecox)
- early castration (before the age of 50)
- extremely heavy climacteric complaints
- reactive depressive emotional deterioration
- complaints due to urogenital atrophy (e.g. colpitis, dry vagina with cohabitation difficulties, urethro-cystitis, incontinence)
- atrophy of skin and mucosal membranes causing complaints
- hirsutism-virilism caused by androgen-estrogen imbalance
- multiple risk factors for osteoporosis
- manifestation of osteoporosis
- hyperlipidemia (LDL elevated, low HDL values), homocystein elevation, risk factors for heart attack
- cognitive disturbances
- manifestation of Morbus Alzheimer in the family

Bleeding disorders

One of the main concerns in the premenopause is the treatment of frequently occurring dysfunctional bleeding disorders, mainly spottings, before and after menstruation, metrorrhagia, hypermenorrhea, menorrhagia and irregular, mostly prolonged cycles. These are mainly caused by luteal insufficiency and missing ovulation and are correlated with an abnormal endometrial structure (often glandular cystic hyperplasia). For the treatment of these bleeding disorders the administration of a progestogen from day 12 to 25 or of a sequential therapy is indicated.

In some cases of heavy bleedings with anaemia the induction of a therapeutic amenorrhea by administration of high dose progestogens can be indicated – if organic causes were excluded beforehand – to give the patient a chance to recover meanwhile. A dose

of 5 to 10 mg of norethisterone acetate or lynestrenol is often sufficient to induce and maintain amenorrhea. When applying GnRH to obtain amenorrhea it should be taken into consideration that a loss of bone minerals is to be expected when administered over more than half a year.

Climacteric complaints and their treatment

The symptomatic treatment of climacteric complaints is the main task of management during the perimenopause. In the beginning hot flushes, perspiration, heart beat, sleeplessness and depressive mood occur most frequently. They will be increasing during the first 3 to 5 years. Five to ten years after the menopause atrophic changes in the uro-genital tract will appear more frequently. The severeness of the complaints and the grade of suffering induced by these will determine the indication for a treatment, e.g. the answer to the question which patient will need hormonal substitution in order to eliminate the existing serious climacteric symptoms (table 2). The success of a hormonal treatment usually shows up after a few days (hot flushes, perspiration) or weeks (sleeplessness, depressive mood, atrophic changes) (see also table 10). As long as hormones are taken, these complaints disappear completely or at least to such an extent that they do not influence the well-being any longer. The treatment of the climacteric syndrome is one of the most successful therapies that modern medicine could offer. After 5 years of treatment – when the climacteric complaints have completely vanished – the continuation of the substitution aims more and more to the prevention of postmenopausal age changes and age related diseases, if indicated.

Indications for a long-term substitution

Which patients should receive a long-term substitution? Can we recommend it to every woman in her postmenopause who does not offer any contraindications? The indications result from

Table 3. Absolute indications for a long-term substitution with estrogen-progestogen

Preconditions: So far well tolerated substitution without side effects and with a good effectiveness.

Risk for

- **Cardiovascular diseases**

  High risk: Angina pectoris, ST-depression of echocardiogram (ECG). Coronary stenosis, hyperlipidemia, (high LDL, low LDL), hyperhomocystinemia, high Apo(a), proven atheroclerosis, myocardial infarction in the family history (direct line).

- **Osteoporosis**

  High risk: Bone density > 1 SD below the mean age related value. Hints from anamnesis: late menarche, pubertas tarda, long lasting primary or secondary amenorrhea without substitution, underweight, state after bone fracture without plausible reason. Osteroporosis in the familiy (direct line).

- **Deterioration of the cerebral performance:**

  High risk: Deterioration of attention, vigilance, concentration, short time memory, word finding, recall of names, mental fatiguability. Morbus Alzheimer in the family, direct line. Climacteric dysphoria, depressive mood, climacteric sleep disturbances.

- **Complaints caused by atrophy of the uro-genitale, skin, conjunctiva of the eye:**

  Atrophy of the vulva, colpitis atrophicans, chronic urethritis-cystitis, urge incontinence and mixed forms, atrophy of the skin and of mucous membranes, cerato-conjunctivitis sicca, increased levels of androgens, hirsutism, androgenic alopecia (in combination with antiandrogens).

the severeness of the complaints being in need of treatment, the existence of risk factors for osteoporosis, cardiovascular events, and Alzheimer's disease as well as the toleration and the success of the treatment so far (table 3). In the case of an existing indication and if a satisfaction with the substitution is given so far, a continuation in the sense of a long-term substitution can be considered. The problem of a possible increase of breast cancer incidence and thrombosis, as described by some US-American authors, will then have to be discussed for the individual case, taking however into consideration the highly positive total results. This question will be discussed below.

The woman's decision will be based on a competent consultation through her physician, on the degree of mutual confidence, and a mixture of information, misinformation, fears, prejudice, and hopes of the patient and, last not least, on her approach to school medicine, medication in general, and her attitude towards the idea of prevention.

Preconditions for a long-term substitution

In general, a long-term substitution is understood to be the administration of hormones for more than 5 years. Thus the decision for a long-term medication has to be made after approximately 5 years of hormonal substitution, which initially has been applied to eliminate climacteric complaints. Only then the mostly avoidable postmenopausal diseases determined by estrogen deprivation become statistically apparent by increased incidence figures.

This cut-off after 5 years is also made by some physicians because recent studies imply an increase in the occurrence of breast cancer diagnosis after more than 5 years of estrogen substitution. We and other authors could, however, not confirm this increase.

In the majority of cases the hormonal substitution can be carried further on without any detailed explanations. Nevertheless, a revision of the indications and contraindications is essential in every preventive check-up and consultation, as they may be subject to alterations.

The following points of view are to be considered as a condition for the indication of long-term substitution:

- A so far good tolerance and a course of treatment free of complications are evident.
- A distinctively positive response to the substitution (according to Menopause Rating Scale I and II) can be noticed.
- No new contraindications or risk factors have occurred.
- Findings of genital and breast examinations are unsuspicious, especially mammography. No risk in family.
- Existence of risk factors and therefore indications for long-term treatment for disturbances of well-being and diseases, that can be prevented by estrogens, like urogenital disorders, osteoporosis, risk of cardiovascular events, climacteric depressions, cognitive disturbances, Morbus Alzheimer in the familiy history.
- Informed consent of the patient.

Contraindications against estrogens and progestogens

Before taking up the treatment, all contraindications against an estrogen-progestogen substitution must be ex-

cluded in a consultation. At present only the acute thromboembolism, connatal coagulopathy (APC-resistance, factor V-Leiden mutation, sickle cell anemia), receptor positive breast cancer within the 5 years margin, floride hepatitis, and haematoporphyria variegata are considered to be absolute contraindications. In some instructions the Dubin-Johnson and the Rotor-syndrome are also listed. I have, however, never seen these syndromes in my over 50 years of practical experience.

Special considerations are essential for the relative contraindications (table 4). They concern the well-considered dosis, the selection of the right estrogen and progestogen, the sort of application and, if necessary, particular diagnostics, a special supervision, and a supplementary treatment apt to reduce the risks.

An extensive information has to be given in order to obtain the informed consent. All considerations should be documented carefully in the patient's file.

No contraindications are: Otosclerosis, hypertension, hyperlipidemia, diabetes, mild heart failure, state after endometrial and ovarian cancer. Special caution at the beginning of a treatment with estrogens is necessary in the first year after the history of myocardial infarction because of the danger of a re-infarction or a deep phlebothrombosis. A cooperation with the patient's internist is essential. An estrogen substitution is nearly always possible in questionable cases, supposing there exists an absolute indication and if all the means of a differentiated therapy are applied.

In cases of small surgical interventions the discontinuation of the estrogen-progestogen medication is not necessary, whereas this seems advisable in larger surgical interventions with a post-operative rest phase and, if necessary, intensive care or treatment, the more as the anaesthesist will discontinue every medication of non-vital importance anyhow. A short break in the estrogen medication will cause no harm.

Table 4. Contraindications against estrogen-progestogen substitution

Absolute Contraindications

- Acute thrombophlebitis, pulmonal embolism (APC-resistance, factor V mutation). Parenteral estrogen medication is possible in the absence of genetic anomalies of the blood coagulation, after a thrombosis substitution earliest half a year later, if no residual symptoms are present. Status after cerebrovascular event.
- Genetic anomaly (BRCa 1 and 2), severe familial history of breast cancer. Breast cancer, if tamoxifen or SERMs are indicated.
- Haematoporphyria, severe acute liver diseases, acute hepatitis Dubin-Johnson, Rotor-syndrome (very seldom occurring).

Relative Contraindications

- The decision is dependent of the weight of the indication for a hormone substitution. Special considerations are necessary as concerns: dose, mode of application (e.g. parenteral). Addition of the appropriate progestogen. Tibolon? SERMs?, Phytoestrogens? Careful supervision, eventually internistic consilium. Additional advise and treatment with the aim of a risk reduction. Detailed counseling, informed consent of the patient.
- Status after breast, endometrial and ovarian cancer, if patient is doubtful.
- Severe fixed hypertension, status after myocardial infarction (?), after cardiovascular event. Severe diabetes with vascular damages.
- Genetically caused anomalies of lipid status, hypertriglyceridemia
- Pancreatitis, cholecystitis, cholelithiasis
- Cardiogenic and neophrogenic edemas
- Long lasting immobilisation, after trauma, major surgery (parenteral applic. ?)
- Severe epilepsy, severe migraine after receiving estrogens or progestogens
- Fast growing myomas, severe endometriosis, proliferating mastopathy

A contraindication against progestogens represents the meningeoma, as a proliferating effect of the progestogens on this tumor has been described.

Selection of preparations

The bleeding problem

The selection and recommendation of the estrogen-progestogen preparation for the therapy or substitution of a woman, which is seeking advice in her menopause, will be based on the question whether the patient still bleeds, whether her cycle (in the premenopause) is disturbed and has to be normalised and whether she will want to have bleeding maintained or if she will want to continue amenorrhea (in her postmenopause).

For cycle regulations a sequential or a combined preparation will be applied cyclically. Most women want to maintain amenorrhea after their menopause, especially in cases of hypermenorrheamenorrhagias, dysmenorrheas, endometriosis or when suffering from the premenstrual syndrome. The possibilities to maintain amenorrhea in spite of substitution are listed in table 5. Undesirable bleedings during hormone administration have so far been one of the most important reasons, why women discontinued the substitution (see also table 9). A solution to this problem is now luckily in almost all the cases possible by giving combined estrogen-progestogen preparations or tibolone continuously.

If a *combined estrogen-progestogen preparation* is administered continuously, the patient must be especially carefully informed, motivated, and, if necessary, followed up at short inter-

Table 5. The postmenopausal patient does not wish uterine bleedings from hormone substitution: what are the possibilities?

- Estrogen-progestogen combination continuously, e.g. Kliogest or any other tablets or patch combination of both hormones
- Tibolon, steroid with estrogenic, progestogenic, and slight anabolic effectiveness, does hardly induce proliferation of the endometrium and in the majority of cases no uterine bleedings
- Estriol: Does not induce proliferation of the endometrium and no uterine bleedings when administered once per day up to a dosis of 8 mg/day. Estriol does not prevent osteoporosis and has no influence on lipids. Estriol is therefore only indicated, when no risk for osteoporosis exists. Sufficient supply of calcium and vitamine D and sufficient physical activity are essential. Combination of estriol with bisphosphonates and lipid reducing substances is possible.
- Combination of 0.3 mg of conjugated estrogens with progestogen. In cases of unsatisfactory effectiveness addition of dehydroepiandrosterone 25 mg/die possible. Practically no bleedings
- Phytoestrogens (e.g. Genistein, Daidzein in soy and red clover). Do not induce bleedings.
- Estrogen-receptor-modulators (SERM), e.g. Raloxifen. Do not induce bleedings. So far little experience
- Progestogen releasing intrauterine device (Mirena, Schering). Releases levonorgestrel. After several months endometrial atrophy and no longer bleedings in spite of further external estrogen application.
- Alternative intake of sequential tablets (according to Hauser), e.g. tablet 1 (estrogen), tablet 21 (estrogen-progestogen) afterwards 2/20, 3/19 etc. No uterine bleedings. Or accordingly 3 estrogen, afterwards 3 estrogen-progestogen tablets etc. Short-term compromise: Bleedings only every 3 months or after ultrasonic evidence of more than 8 cm endometrial thickness. Protection from endometrial carcinoma through progestogen could not yet be verified in this procedure.
- Endometrial ablation: if indicated. Hysterectomia if also other urgent indications are present.

vals because of the spottings that occur during the first 4 to 6 months and could frequently induce fright of cancer. These initial bleedings occur seldom when the menopause has set in more than 5 years before.

For the recovery and therapy of a patient with Fe deficiency suffering from anaemia after irregular uterine bleeding in the premenopause it is possible to induce a therapeutic amenorrhea by continuous oral progestogen administration, e.g. 5–10 mg of norethisterone acetate or lynestrenol orally daily without interval. If bleeding occurs, the progestogen dosis can shortly be elevated or a low-dose estrogen (0.02 mg of ethinylestradiol) can be administered additionally.

Tibolone can be classified as designer-estrogen. It includes estrogenic and via metabolites progestogenic and slightly anabolic effects in one substance and induces – if so – only a minimal endometrial proliferation and therefore seldom uterine bleedings. Tibolone can, however, result in a weight increase in women with according disposition and in some cases – desired or undesired – increase the libido.

Estriol constitutes a weak estrogen with the limitations in the mechanism of action as shown in table 6, this mainly because of its short time of binding to the receptors and its rapid elimination. Only one dose should be given daily in order to avoid endometrial proliferation and bleedings.

The *selective Estrogen-Receptor-Modulators (SERM)* represent a remarkable development offering important possibilities for a hormone medication otherwise contraindicated in high risk patients (table 6). Other than under estradiol medication the endometrium and breast will not be stimulated. Therefore there are no uterine bleedings. There is also no increased danger of developping endometrial cancer since the endometrium does not proliferate as it would during Tamoxifen medication.

Phytoestrogens seem to be one of the factors also responsible for the low

Table 6. Designer estrogens, selective estrogen-receptor modulators: new possibilities of organ specific hormone therapy and substitution

Classification	Endometrial Stimulation	Breast Stimulation	Heart Protection	Osteoporosis Protection	Neuro Protection	Climact. Complaints
Agonist: Estradiol	Yes	Yes	Yes	Yes	Yes	Yes
Agonist: Estriol	No*	Little	No	No	No	Weak
Partial antagonist: Tamoxifen	Yes (atypical)	No Inhibition	Yes	Yes	No	No intensification
Pure antiestrogens: Toremifen	No	No Inhibition	Yes	Yes	No	No
Selective rezeptor modulation: Raloxifen	No	No	Yes	Yes	No	No
Scavestrogens: 17α-Estradiol and derivatives	No	No	Yes	No	Yes	Yes

* when administered once/day

Tibolon with its estrogenic, progestogenic and slight anabolic effectiveness with little endometrial effectiveness is also a designer hormone

presence of certain carcinomas in some countries with phytoestrogen-rich food intake, e.g. Japan. Estrogens contained in Cimicifuga and soy do not influence the endometrium and the breast. However, phytoestrogens are not sufficiently effective for heavy climacteric disorders. They will nevertheless be sufficiently effective to achieve enough relief of the subjective climacteric complaints in most cases. Phytoestrogens replace the human estrogen from the estrogen receptors of the endometrium and uterus, but do not stimulate them, but they stimulate the beta-receptors, which prevail in the bone and cardiovascular system.

If a patient does not want to take the medication orally, if she is forgetful, prefers injections, or if a parenteral medication with short-term controls is medically required, a combined medication of 4 mg estradiol valerate and 200 mg dehydroepiandrosterone (DHEA) is available offering an effect of 3 to 4 weeks when injected intramuscularly. DHEA, a mild anabolic steroid of the adrenal cortex, is supposed to have a slight psychotropical effect, it influences the lipid metabolism positively and is presently discussed as an anti-aging therapy, for which, however, the dose is most likely too low.

The commercially available *estradiol-testosterone combinations* (4 mg estradiol valerate and 98 mg testosteron-enanthate) are especially indicated in women with climacteric complaints and additional psychoasthenia, apathetic depressive mood, libido-disturbances and anorgasmia.

Both injection-preparations lead to a proliferation of the endometrium after a few months, so that oral gestagen application under sonographic control becomes necessary to induce transformation and withdrawal bleeding of the endometrium.

Diet against Climacteric Complaints

According to the study results at hand it will also be possible to treat climacteric complaints by dietary measures. Resorption investigations and plasma level determinations have shown that the application of isoflavons and lignanes and the application of glycosid conjugates of genistein and daidzein lead to tissue levels of effective phytoestrogens in a therapeutic range to eliminate subjective climacteric complaints. The binding to SHBG is low so that the main amount of phytoestrogens is available in free form in reference to an increase in estrogenous effective enterolactons and enterodiols. Linseeds (rap seeds), asparagus, carrots, broccoli, and soy were especially effective, whereas the bran and soy contents in nuts and legumes elevate especially the estrogenous effective isoflavone concentrations of enterolactone and enterodiol. Concentrations of 70 nmol/litre daidzein and of 200 nmol/litre enterolactone are suitable to reduce climacteric complaints. To my experience these levels can be achieved through a diet consisting of 500 ml of soy milk, soy bread and soy margarine, wholemeal products, linseed oil, soy sauce, tofu, miso, asparagus, carrots, broccoli, oats, and green tea.

Further investigations will have to prove to which extent the heaviness of climacteric complaints in different women can be influenced by a diet, which of the commercially available foods contain phytoestrogens or their precursors, and in what amount and in which way the intestinal flora is necessary or helpful for their effectiveness. Finally, it remains to be investigated, which desirable effects of the human estrogens can not be achieved by phytoestrogens and which so-far unknown side effects they may induce.

Forms of Application

There is a wide range of preparations, their dosage and application forms which are offered commercially at present. Estrogen medication can be performed by oral, lingual (drops), transdermal administration (patches, gel) and by injection. For individual treatment nasal sprays, vaginal ointment, ovulas, suppositories and other regional application forms can be prescribed. The pros and cons of the different applications forms are shown in table 7.

The special indications for a transdermal application of estrogens are shown in table 8.

The numerous available artificial progestogens can be administered orally. Micronized progesterone can be applied orally and vaginally as capsulas. Progesterone can be applied vaginally in the form of gel where the progesterone is resorbed almost exclusively by the endometrium (so-called organ-near, organ-selective application form). Progestogen suppositories of 200 and 400 mg can be obtained from England via

Table 7. Advantages and disadvantages of different application forms of estradiol and progesterone

Estradiol

Oral:

- Advantages: Because of the first liver passage strong favourable effect on lipids (HDL and LDL, homocystein, Apo(a)). Preventive effect against atherosclerosis and consequent diseases. Strong increase of SHBG, very favourable in cases of virilization because of binding of free androgens.
- Disadvantages: Increase of triglycerides, of renin substrate, renin, some coagulation factors

Parenteral (transdermal, intramuscular, lingual, nasal application):

- Advantages: Bypass of the first liver passage, no significant influence on coagulation, triglycerides, renin substrate, renin. Favourable for patients at risk of thrombo-embolism, hypertension, stroke, liver diseases, gall bladder, stomach- and intestinal diseases, diabetes.
- Disadvantages: Reduced increase of HDL and reduced decrease of LDL, increase of IGF (?). No increase of SHBG. When patches: hypersensivity reactions of the skin.

Local application (ointment, ovula):

- Advantages: No load of organs (liver, gall bladder, stomach), no metabolic effect, if not desired. Low doses sufficient. Organ-near, organ-selective therapy.

Progesterone

Oral:

- Advantages: Orally effective, naturally occurring hormone, exerting its physiological effects.

Vaginal (Suppositories, capsulas, vaginal gel):

- Advantages: Effective resorption and tolerability, predominant flow towards endometrium. Less hepatic metabolisation.

Local:

- Advantages: Application directly to the breast: Effective local resorption, local physiological concentration in breast tissue. Significant antimitotic effect. No gereral effects in the organism.

Table 8. Special indications for the transdermal (transcutaneous) application of estrogens

- Aversion against oral intake or taking of numerous oral medicaments. Mutual influence on effectivity of medication.
- Hypersensitivity of the stomach: gastritis, ulcus ventriculi, status after stomach surgery
- Intestinal diseases, disturbances of resorption. Allergy against added substances (e.g. colour substances, resorption enhancers a.o.)
- Liver diseases: hepatitis. Status following hepatitis, chronic disease. Cirrhosis, alcohol-liver. Hematoporphyria.
- Gall bladder diseases: cholecystitis, cholelithiasis. Pancreatitis
- Hypertriglyceridemia, esp. Type I and V Frederickson. Combination with nor-testosterone-progestogens acts favourable.
- Hypertension: labile and fixed.
- Treatment with thyreoid hormones, biochemic thyreoid testing.
- Heavy smoking (no decrease of estrogens in blood). Alcoholism (no increase of estrogens in blood).

the international Pharmacy (Cyclogest, Hoechst). The injection of 17α-Hydroxyprogesterone is usually applied in the perimenopause.

Compliance Adherence: Intake-Reliability and Treatment-Loyalty

The observance of medical prescriptions is highly dependent from the patient's motivation, which is based on the heaviness of the climacteric complaints and the fast reduction of the complaints through the hormone preparation, however also dependent from the heaviness of the fears and the objections of the woman. The quality of the information and the conveyance of competence through the physician can reduce many an uncertainty. More frequently than the seldom occurring and minor side-effects of the estrogen and progestogen medication, the fear of side-effects and the mostly unjustified warnings through uninformed physicians, friends, or the negatively critical newspaper reports lead to an early discontinuation of the hormone medication even when minor problems occur. The main reasons for the breaking-off are fear of cancer, undesired uterine bleedings and objections in reference to a possible weight gain. The instructions of the preparations also represent a big problem (table 9).

Whereas many women principally refuse any kind of hormone medication for reasons of prejudice against something seeming unnatural or dangerous, up to 30% of the women do not begin medication after the hormones have been prescribed. Some statistics show that 30–50% of the patients have not begun taking their hormones one year after prescription or stopped taking them for reasons of unsufficient care and being left alone with their mostly irrational fears. It is then seldom possible to get a patient to take hormones again. The best statistics show that after more than 10 years 30% of the women of the original total still take their hormone preparations, 15% of which have changed to another preparation or altered the dosage. The main reasons for breaking off the estrogen-progestogen medication are shown in table 9.

The poor results effecting adversely the genuine preventive long-term substitution make it necessary to deal urgently with the problem of compliance or adherence in order to ward off physical disadvantages from the patients and to prevent economical damage.

Table 9. Reasons given by postmenopausal women in % for discontinuation of estrogen-progestogen substitution (within first year)

	Oral sequential therapy	Patches + oral progestogens	Estrogen-progestogen continuously
Instruction leaflet	23	16	10
Strong or prolonged bleedings	8	8	0
Intermenstrual bleedings	4	5	21
Breast complaints	2	6	14
Edemas, heavy legs	2	3	8
Headache	2	4	4
Nausea	2	4	6
Free of complaints	47	15	11
Too much medication	3	6	9
Press reports	6	7	5
Discontinued by physician	5	6	11
Change to other medication	4	8	0
Skin irritation	–	15	–

An increase of compliance can be achieved by:

- Good guidance of patients
- Thorough information
- Gaining the patient's insight into causes and possible subsequences of the climacterium and the advantages of the substitution
- Accepting the physician and his competence
- Written instructions
- Second consultation within the first 6 weeks
- Regular check-ups
- Initiation to read books and brochures on the topic
- Quick and competent reaction to negative and uncritical information in newspapers
- Taking preparation always at the same time of the day, preferably in combination with other regular actions like breakfast etc.
- Memo packages
- Simple and agreeable application without side-effects
- Not too many preparations at the same time
- Quick and clear reduction of the complaints through medication
- Increase of complaints without medication
- Membership in patients' self-help groups

Table 10. Success of oral estrogen-progestogen substitution in typical climacteric symptoms

Complaints	Free of complaints in % or clear improvement	
	After 1 week	After 6 weeks
Hot flushes, perspiration	91	98
Palpitation of the heart, irregular heart beat	78	92
Nervosity, irritability, anxiety	72	95
Tiredness, inefficiency	74	97
Sleeplessness	77	92
Depressive mood, lack of drive	62	87
Muscle and joint complaints	66	85
Dry vagina, cohabitation disturbances	61	100
Complaints of urinary tract	54	89
Urinary incontinence	12	74

Success of Treatment

Vegetative Complaints

The typical vegetative complaints like hot flushes, perspiration, palpitation of the heart and vascular disorders of the upper extremities, including indisposition, are based on an increase in estrogen deficiency during perimenopause, being below the limit of the vegetative stability regulated by the hypothalamus with the help of estrogens. These subjective symptoms respond to an estrogen therapy according to the cause and effect-principle in 90 to 95 % of the patients with a complete removal or a clear reduction of the complaints within 7 days to maximally 6 weeks (table 10). In the case of a non-response the diagnosis must be verified and, for example, hyperparathyreodism, any other vegetative dysfunction or psychogenic problems, especially masked depressive mood, must be excluded.

In any other frequently occurring complaints like nervousness, irritation, sleeplessness and depressive moods the origin is more complex and strongly individual. However, these symptoms are equally eliminated in a high percentage by estrogen administration, when

the typical main complaints have vanished. In some cases the tranquilizing effects of progesterone can specifically included in the treatment.

Objectivation of the Heaviness and Reduction of the Climacteric Complaints

For the objective evaluation of the climacteric complaints the Kuppermann-Index has so far been used where a number of typical (and also untypical) complaints are evaluated in the view of their heaviness with a random multiplication. Older study-results can be compared with this system. This index has correctly been critisized and meanwhile been abandoned because of its partially questionable weighing, its insufficient specifity, its lack of important symptoms and the badly differentiated summarizing of the complaints.

In 1994 experts from Switzerland, Austria and Germany have therefore established new rating scales for climacteric complaints having taken into consideration these points of critics. The Menopause Rating Scale I (MRS I) gives information about vegetative complaints before and after the treatment. The MRS II quantifies the different stages of indisposition which determine the quality of life. The reliability and the practically relevant information of the capability of this method has been verified in a representative random control of 479 perimenopausal patients (figures 1–3).

In contrast to the Kupperman-Index the MRS does not include the symptoms of paraesthesia, dizziness, headache and formication, as these are considered to be irrelevant and unspecific by the authors of the MRS. The increase of slight, medium, and especially heavy complaints in women investigated with MRS resulted especially from the addition of the symptoms fear and sexual problems (alteration of sexual desire, sexual activity and satisfaction) and the extension of the term cardiac disorders from palpitation of the heart (Kupperman) to cardiac oppression (angina pectoris) and arrhythmias, mostly the result of postmenopausal hypertension.

Urogenital Complaints

These occur only several years after the menopause, when estrogen levels have become extremely low and the estrogen

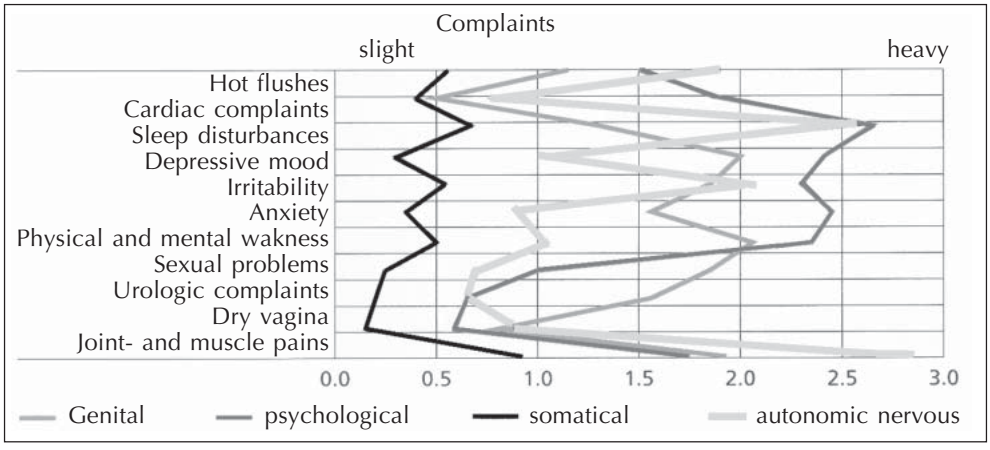

Figure 1. Menopause Rating Scale I (MRSI) Typology of Complaints

deficiency has become chronical. Complaints like atrophic colpitis, urethrocystitis, urge- and stress-incontinence, often combined, dysuria, stranguria, and urethral prolaps can successfully be prevented or treated to a high percentage by oral estrogen substitution or local estrogen application. Progestogens can additionally strengthen the connective tissue and the sphincter urethrae (table 11).

Skin and Mucosa

The skin and mucosa become atrophic under estrogen deficiency. Their vascularity, ability of water binding and elasticity decrease. The administration of estrogens results in an increase of epidermic thickness, a decrease of the depth of wrinkles and an improvement of the vascularity, ability of water bind-

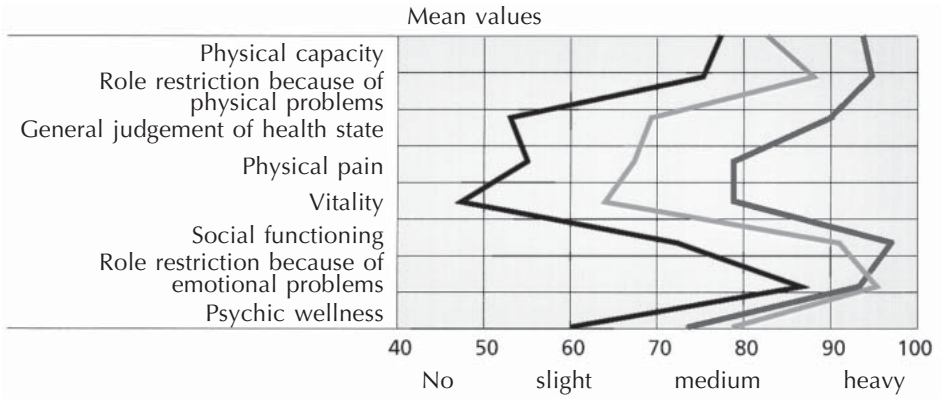

Figure 2. Menopause Rating Scale II (MRS II): Health related Quality of Life

Which of the following complaints do you suffer from at present
Please make a cross for each complaint, how strongly you are affected.
If a complaint is not existing, please make a cross at "no"

	No	very slight	slight	medium	heavy	very heavy
Hot flushes, sweating	☐	☐	☐	☐	☐	☐
Cardiac complaints (Palpitations, tachycardia, irregular heart beat, angina pectoris)	☐	☐	☐	☐	☐	☐
Sleep disturbances (Difficulties to fall asleep, to sleep through, early awakening)	☐	☐	☐	☐	☐	☐
Depressive mood (Despondency, sadness, tearfulness, loss of drive, mood changes)	☐	☐	☐	☐	☐	☐
Irritability (Nervousness, mental tension, aggression)	☐	☐	☐	☐	☐	☐
Anxiety (Internal restlessness, panic)	☐	☐	☐	☐	☐	☐
Physical and mental exhaustion (General decrease of performance, decrease of recall, decrease of concentration, forgetfulness)	☐	☐	☐	☐	☐	☐
Sexual problems (Changes of sexual desire, of sexual activity and of sexual satisfaction)	☐	☐	☐	☐	☐	☐
Complaints of urinary tract (Complaints in micturition, dysuria, incontinence)	☐	☐	☐	☐	☐	☐
Dry vagina (Feeling of dryness or of burning, complaints during intercourse)	☐	☐	☐	☐	☐	☐
Complaints in joints and muscles (Pain in joints, rheumatic complaints)	☐	☐	☐	☐	☐	☐
No of point	0	1	2	3	4	5

Figure 3. Menopause Rating Scale II (MRS II): Scale of Self Assessment

ing and elasticity by stimulating the hyaluronic acid and the collagen tissue.

Cognitive Functions, Morbus Alzheimer

In the postmenopause and senium the cognitive functions like attentiveness, powers of concentration, vigilance and short-term memory decrease distinctively. It has been shown that these higher human functions, that are most important for the preservation of the personality and the ability of communication, can be preserved or even re-established by the postmenopausal administration of estrogens. These effects are probably based on the improvement of the cerebral vascularity (NO) and a positive influence of the acetylcholine and tryptophan-serotonin metabolism. Possibly neurosteroids and neuroproteins play a so-far unknown role in this connection.

The occurrence of the Alzheimer disease increases clearly in correlation with the increase of age and is found 2 to 3 times more often in women than in men. It leads to a complete loss of cognitive functions and personality structure with regression in a complete dependence from the nursing persons. Several case studies have shown that a postmenopausal estrogen substitution can avoid or at least postpone the development of the Morbus Alzheimer, dependent from the duration and dosage of the estrogen intake, in 30 to 60% (table 12). This preventive effect is a very strong argument for a preventive long-term medication with estrogens.

It is possible to improve in a modest range some of the cognitive functions in patients with an existing or developing Morbus Alzheimer in a not too severe form by long-term estrogen administration. The effect is based on the inhibition of the amyloid-precursor proteins, which are typical for the Morbus Alzheimer and which are the precursors of the Alzheimer-plaques. The effect also derives from the maintenance of the cholinergic system, from the positive effect on the apolipoprotein E and the cholesterol-synthesis, an optimation of the cerebral glucose-insulin metabolism, and finally from the modulation of immunologic proceedings and the neuroprotection and the increasing effect of estrogens on neuronal plasticity.

Table 11. Incidence of genital inflammation and functional disturbances during estrogen substitution in comparison to non-substituted postmenopausal controls (252 patients, Dept. Obstet. Gynecol., University of Ulm)

Diagnosis	With estrogen	Controls without estrogen
Dry vagina	0	31
Senile colpitis	2	61
Mixed bacterial flora	13	96
Monilia, hyphae	1	29
Trichomonas	2	17
Papanicolaou grade I	128	104
Papanicolaou grade II	2	22
Pollakis-dysuria	0	13
Urge-stress incontinence	10	33

Estrogens and Diabetes Typ II

There is an elevated disposition to develop a relative insulin resistence (insulin requirement of more than 200 E/day) in the postmenopause in cases of a respective genetic, endocrine and metabolic predispostion. It results in a hyperinsulinemia with decrease of the insulin receptor density, which can become the prestage of diabetes mellitus of the type II. The hyperinsulinemia is also responsible for the existence and development of atherosclerotic vascular wall alterations. Be-

sides the increasing age mainly the android adipositas (waist-/hip-quotient increased), the decrease of estrogens with predominance of ovarial and adrenal androgens, the decrease of growth hormone secretion, the increase of the cortisol activity and an increase in the concentration of the free fatty acids are responsible for this metabolic syndrome.

The decrease of estrogens induces a decrease of the sexual hormone binding globulin (SHBG), which is normally produced under estrogen influence in the liver. This results in an increase of the free, also biologically active androgens. These decrease further the production of SHBG and block furthermore the insulin receptors in the membrane of the liver cells, muscle cells, and fatty cells.

The administration of estrogens can break through the insulin resistence when oral application is chosen, which – in contrast to the parenteral application – leads to an increase in SHBG production. The long-term oral estrogen substitution (preferably in a combination with the progestogen cyproterone acetate) induces a reduction of the free androgens, a decrease of the insulin level and a stimulation of the binding proteine 3 for the insulin-like growth hormone (IGFI). Thus, the oral estrogen has a counter-effect on hyperinsulinemia, the development of old age diabetes and the atherosclerosis.

Since androgens improve the insulin resistance, the administration of estrogens in combination with progestogens, which exert a residual androgenic effect, is not recommendable.

The metabolic processes, as described here, also represent risk factors for the development of endometrial and breast cancer.

Obviously a part of the atherosclerotic and diabetic diseases with their various consequences can be avoided by a long-term substitution of estrogen-progestogens and thus not only a lot of grief can be spared, but also a substantial amount of money can be saved – another important argument for the

Table 12. Prevention of Alzheimer-disease through estrogen substitution in women in their postmenopause in comparison to untreated controls: influence of dose and duration of medication

Tang et al. 1996

Groups	Cases	Number Alzheimer patients	Not ill	Relative risk	50% Confidence-Interv.
No estrogens	968	158 (16.3%)	810	1.0	–
< 1 year estrogens	31	3	28	1.3	0.40–4.20
> 1 year estrogens	58	1	7	0.47	0.02–0.92

Paganini-Hill 1995	Relative risk
Untreated controls	1.0
Preventive estrogen substitution	0.89
Duration of treatment with estrogens	
< 7 years	0.74
> 7 years	0.49
Dose of estrogen	
0.625 mg conjug. estrogens	0.59
1.25 mg conjug. estrogens	0.46

postmenopausal administration of estrogens.

Oral estrogen substitution is obviously not contraindicated in existing diabetes, moreover the glucose tolerance and glucose utilisation are improved. On top of this the sensitivity of fatty and muscle tissues to insulin is improved through the production of insulin receptors. Estradiol is to be preferred to conjugated estrogens and pure progesterone is recommended for progestogen addition.

Sexuality

More than half of the women in the postmenopause experience a significant reduction of sexual desires and events. There are various causes: age, diseases, general limitations of fitness (also of the partner) may play a role. On the other hand it is understandable that a woman suffering sleeplessness, depressive moods or a dry and atrophic vagina with respective complaints, cystic pains or incontinence is no longer interested in sexual activities. Some women will most certainly use their menopause as a most welcome excuse to terminate their sexual duties. Estrogens have no direct influence on the sexuality. However, the above mentioned uro-genital complaints can be removed by estrogens and thus the former sexual behaviour can in these cases sometimes be re-established. The libido is, also in women, dependent from the androgen level. In cases of libido deficiency and anorgasmia sometimes an androgen preparation, e.g. testosterone capsulas (2–3 times 40 mg undecanoat per day) or better 100 mg to 250 mg of testosterone depot (enanthate) intramuscularly injected every 4 weeks can help.

The information about possible virilizing side-effects (deepening of the voice, hair on the upper lip) and, if they occur, the immediate breaking off of the treatment is essential to avoid harm for the patient and possible legal consequences.

Metabolic Effects in long-term Substitution, Atherosclerosis

The main arguments for the long-term substitution with estrogen-progestogens, as strongly recommended by all the experts, are the numerous positive metabolic effects of the estrogens causing well-being and a high quality of life and enabling the prevention of a high percentage of avoidable diseases with all their effects in the third life decade.

The estrogens have a preventive effect on the development of atherosclerosis in the animal experiment and in humans. This derives from their positive effects on the lipoproteins with a decrease of the atherogenic LDL and their oxydation products and an increase of the antiatherogenic HDL, from the increase of organic vascularity among others via an increase of the NO-production (also in coronaries and cerebral vessels), from the block of the calcium channels with the decrease of the blood pressure and from the improvement of the blood flow quality. The amount of atherosclerotic plaques becomes reduced. These positive effects caused by estrogens result in an up to 50% reduction of the incidence and the mortality for cardiovascular events (Table 13).

Estrogens even protect smokers from cardiovascular events, even though not quite as effectfully as non-smokers (RR 0.8). These positive effects on the most frequent public diseases, also representing the most frequent death causes, far more frequent than cancer diseases, are actually sensational. It is hard to understand why the public does not

accept them with more enthusiasm. Osteoporosis, too, with its consequent bone fractures, can be avoided in 60 to 90%, according to localisation and hormonal dosage, or can successfully be treated up to the high age in a not too advanced state.

The most frequently occurring complaints in the small joints of the upper and lower extremities during the climacterium usually disappear quickly after estrogen substitution. The positive effect on the mucosa and the cosmetic effects on the skin and its appendages represent another convincing argument for a long-term substitution.

Benefit / risks, costs of long-term Treatment

Numerous authors have tried to set advantages off against possible disadvantages of the estrogen-progestogen substitution with the aid of mathematical methods. Such calculations are necessary in the sense of "evidence-based medicine" when a long-term treatment has be recommended with good reasons. The profit must in any case surpass by far the risk. The profit of the treatment of climacteric complaints and symptoms caused by atrophic changes are undisputed. A long-term treatment is one with a duration of more than 5 years. The continued long-term treatment has the important goal of the prevention of postmenopausal diseases being in direct or indirect connection with chronic postmenopausal estrogen deficiency.

Table 13. Favourable influence of oral estrogens (1.25 mg conjugated estrogens) on blood levels of cholesterol and its fractions: reduction of risk for cardiovascular events and their mortality. Data from international literature

Decrease of total cholesterol levels	5–7%
Decrease of LDL levels	15–25%
Increase of HDL levels	15–30%

Inhibition of LDL-oxydation, increase of LDL-receptors, increase of Apo 1 and Apo 2, increase of triglycerides

	Incidence	Mortality
Decrease of cardiovascular events	30–50%	25–35%
Decrease of apoplectic events	0–20%	20–30%

Progestogens – except for progesterone and its derivatives – slightly deteriorate lipid values, however they have little influence on long-term clinical data or on incidence and mortality

A risk reduction of osteoporosis and bone fractures and of angina pectoris with cardiovascular events of about 50% can be regarded as saving of costs owing to illness, loss of working hours and expenses for rehabilitation or need of care. Furthermore, the reduction of cardiovascular events of 20 to 30% in correlation with the reduction of mortality in the event can truly be calculated as cost factors. This also applies for the prevention or the postponing of Morbus Alzheimer and finally for endometrial, ovarian (in some long-term studies) and colon carcinoma and their mortality and the reduced cancer incidence altogether under a long-term substitution.

Concerning the risk of breast cancer most investigators have calculated a slight increase in the diagnosis. I refer the reader to the chapter of Schneider and Jackisch. The same applies for the number of abrasiones, hysterectomies and breast operations. It has to be added to the costs that women under substitution go more frequently to check-ups, have more often a mammography performed and on the average live longer.

Naturally it is difficult to quantify the additionally achieved elimination of

the different complaints, the improvement of the well-being, the cognitive abilities, the improvement of the sexuality and the quality of life. It has however been tried to evaluate these imponderables with the aid of the so-called quali factors.

Result of the Cost-Benefit Calculations

In spite of the intimated difficulties, all authors are in accordance with the overwhelmingly positive result of the considerable value and the recommendability of the preventive long-term treatment with estrogens and progestogens for the health and well-being of the women under substitution against those without substitution. These results can be understood and count as a safe basis for therapeutic recommendations in the particular case.

At the same time it could be proven without any doubt that the prevention with estrogens has a considerable cost-saving effect which should be an important argument for the investors and the legislative in the present times of financial problems of our health system.

Duration of Treatment

It has to be clearly distinguished between a short-term symptomatic therapy of climacteric complaints and a long-term preventive substitution. The treatment of climacteric complaints will last as long as they persist, e.g. 3 to 5 years, seldom longer. The long-term preventive substitution will follow, if indicated, and last, in some extreme cases, till the end of the life.

To achieve a significant, provable effect on the risk of cardiovascular events caused by atherosclerosis a treatment of at least 5 to 10 years is essential. The effect will maintain for a number of years and will wear off eventually within 10 years. To avoid osteoporosis and bone fractures a substitution of at least 15 to 20 years is necessary as bone loss will resume immediately upon withdrawing from hormonal treatment.

As a result of some studies, which report about an increase of breast cancer diagnoses after estrogen or estrogen-progestogen treatment over more than 5 years, some therapists recommend the limitation of the substitution to 5 years or they ask for a benefit-risk evaluation after 5 years before continuation of the treatment. Such a consideration should, however, be made upon every new prescription. An increase of the breast cancer risk could not be found by us in our 25-year study and quite a number of other investigators also failed to find this increase. Therefore the risk – should there be any – is rather low and probably limited to a faster growth of existing smaller carcinomas by the administration of estrogens. This is suggested by the lower malignity, the higher rate of cure, the lower death rate for cancer, and finally the reduction of endometrial and colon cancer incidence under an estrogen-progestogen substitution.

For the practical argumentation see the chapters benefit-risk and estrogens and cancer.

Morbidity, Mortality and Life Expectation

The average life expectation of a woman has not least on account of the progress in modern medicine gone up from a range of between 40 to 50

years in the 19th century to now 80 years. This prolonged period of life is not only based on the reduction of mother and child mortality and the victory over the big epidemics, but also on the success of prophylaxis and treatment in high age. Accordingly, due to the increasing number of old people, expecially old women, an increasing number of women over 50 in their third life decade have to live without the important benefit of estrogens, if the missing hormone is not substituted. The same medical scientists, who have given humans a prolonged life expectation, consider it their responsibility to make this period worth living, to keep away unnecessary complaints, diseases and suffering and to bring the terminal illness leading to death as close as possible to the moment of the natural death. This is called the "compression of morbidity" and disablement. The possibilities of "anti-aging" and life prolongation have recently been added.

It has been found in comparing statistics that an early death of about 6,000 to 8,000 women per 100,000 per year in their postmenopausal decade (depending on an optimistic or pessimistic evaluation of the preventive effect) could be avoided by long-term preventive estrogen-progestogen substitution. Those women, who get a long-term preventive estrogen substitution, have accordingly a longer life expectation of 2 to 3 years than those without substitution.

Women's State of Information, Statistics for Estrogen Intake

In Germany the knowledge of the different processes of the menopause and the possibilities of an estrogen treatment is quite good in comparison to other countries. Almost 80% of the women are sufficiently informed. Another 80% of them got their knowledge through the media, 40% through women friends, relatives and women's groups and 44% through physicians, however only after specific inquiry (International Health Foundation, 1992).

In Germany, almost 30% of the women in their menopause take estrogens (IHF, 1992). These findings were confirmed in the Berlin Women's Study (Schultz-Zehden, 1998). The intake rate was approximately about 26% with a maximum between 55 to 59 years and 38% with a subsequent decrease to about 10% at the age of 65 to 70 years. This medication rate is the best in Europe.

The duration of intake, however, is unsatisfactory, as the majority of the patients have stopped the treatment already 5 years after beginning. The target of the prevention through a long-term intake is only achieved by a very low percentage of the women. The reasons for this are mainly undesired bleedings, weight increase and fear of an increase of cancer risk and the poor engagement of many physicians to recommend long-term substitution.

Costs

20% of the total expenses for medical care apply to the treatment of women after the menopause suffering from a disease caused mainly by estrogen deficiency (Wren, 1987). 40% of these care costs could be avoided by estrogen-progestogen substitution of all women in their postmenopause (Fioretti et al, 1978).

The expenses of DEM 15,– to 30,– per month for the substitution with hormones are rather low, considering hospital treatment costs up to DEM

600,– per day in addition to considerable costs for drugs, medical instruments and medical treatment.

The core of such a cost calculation is shown in figure 4. The number of years worth living gained by estrogen substitution should be most convincing for every woman and her consulting physician having to decide pro or contra long-term substitution.

Conclusion

The estrogen-progestogen substitution in the peri- and postmenopause is an extremely effective, well-tolerated and low-risk procedure. Hormone replacement can protect women from climacteric complaints and uro-genital complaints, based on atrophic changes after the loss of ovarian hormonal function in their third life decade. Estrogen substitution can also partially avoid an early loss of the physical and mental ability of high age and can also give the chance of the prevention, decrease or postponing of a number of fate determining diseases like osteoporosis, cardiovascular events, Alzheimer disease or colon cancer.

This and the improvement of the subjective well-being and the cognitive abilities lead to an improvement in quality of life and the possibilities to create a life-worth living in high age together with the prolongation of life expectation. The possible side-effects and risks of the estrogen-progestogen substitution are very low. They can furthermore be clearly reduced by a competitive and sensitive treatment and consultation about the various changes in preparation, dosage, compounds and means of application at hand.

New possibilities of the substitution without uterine bleedings were established by a continuous combination of estrogen plus progestogen, by selective estrogen-receptor modulators and by phytoestrogens, thus eliminating an important reason for the drop out from hormone intake of many women. An improvement of the instructions that do not frighten or disinform patients is another important demand.

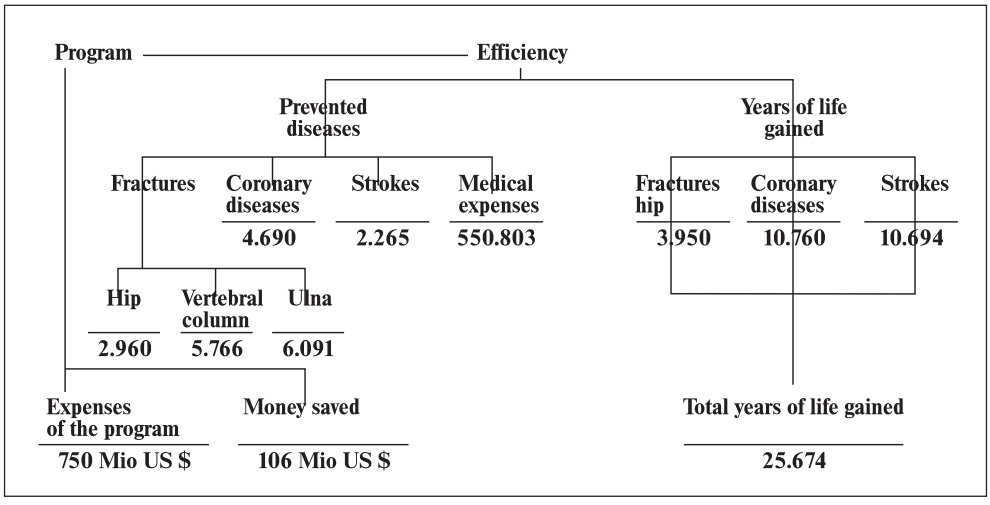

Figure 4. Favourable effects of a long-term estrogen substitution upon preventions of diseases. Years of life gained and money saved per 100 000 women/year (redrawn from Tieffenberg et al, 1994)

The fear of the women of a positive influence of the estrogens on the occurrence of cancer is presently an important impediment for the acceptance of the estrogen substitution. The physician's rational arguments are usually little successful.

New developments in the area of the selective influence of estrogen-receptors and the phytoestrogens seem to bring this problem closer to a solution. The combination of progestogens with the estrogens results in a decrease of endometrial carcinoma and, as shown in long-term studies, also ovarian and colon carcinomas. Some investigators assume a slight increase in breast cancer diagnoses. Other investigators could not find this. Altogether, the total number of cancer diseases and the mortality of cancer do decrease clearly under estrogen-progestogen substitution.

In view of the obvious advantages of the estrogen substitution for women it remains hopeful that in future more women in their postmenopause decide for a long-term substitution than this is the case at present. At present, the long-term prevention with estrogens practically plays only a small role in Germany and Europe. Every woman should have the right to possess all available information about the estrogen-progestogen substitution at the beginning of the menopause in order to decide competitively on the basis of a genuine knowledge and deepened understanding whether she will want to take hormones or not. The long-term prevention with estrogens and progestogens is without any doubt one of the most important improvements of the preventive medicine during the last decades. It represents at any rate an attractive scientific offer with unimaginable perspectives for the future.

Gynecologists are asked to deal intensively with the prophylaxis and treatment of women in their third life decade and to cooperate closely with those adjacent medical disciplines, where estrogens have a preventive influence. These are mainly diseases in the area of internal medicine, geriatrics, surgery and orthopedics.

The increasing number of old women in human society demands for the develompent of a specific old age gynecology in order to better cope with the new and improved possibilities of science and the desires, demands and fears of patients. The existing possibilities of the prevention of cardiovascular, cerebral and carcinogenous diseases must definitely be made practical. Gynecologists must be made "doctors for women's health". Preventive gynecology must replace reparative gynecology as far as possible. This does not only avoid much human grief but is, in my opinion, the only possibility to solve the urgent financial problems of the public health system.

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