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Postmenopausal Hormone Therapy

Impact on Menopause-Related Symptoms, Chronic Disease and Quality of Life

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Abstract

Quality of life in climacteric and postmenopausal women is often compromised. This overview addresses the many factors that may interfere with health and well-being in such women. Hormonal changes during the menopausal transition, finally resulting in estrogen deficiency, play a pivotal role in the incidence of climacteric symptoms and also in the development of chronic diseases. Such

symptoms and diseases can contribute to impaired quality of life in climacteric and postmenopausal women. Postmenopausal hormone therapy (PHT) is the treatment of first choice to alleviate symptoms of estrogen deficiency. Besides effectively relieving climacteric symptoms and complaints, PHT can also protect against some chronic diseases, such as osteoporosis and colorectal cancer.

Presently, available PHTs vary widely in type, estrogen and progestogen dosage, and route and duration of administration. Furthermore, the number of alternatives to treat climacteric symptoms, and/or to prevent chronic diseases, has increased. Therefore, doctors involved in the care of climacteric women in the 21st century are much more able to meet the specific needs of individual patients and improve health and quality of life.

Menopause is the time of a woman's last menstrual period. It is an important milestone in a woman's life. It means the end of, on average, 40 years of menstruation, which for many women is a monthly burden, especially when entering the perimenopausal years.[1,2] However, menopause is also the definite beginning of infertility, which may come as a serious frustration for women who have remained childless, sometimes after years of unsuccessful intervention. Directly or indirectly because of hormonal changes related to ovarian aging, climacteric women are susceptible to one or more physical and psychological symptoms or complaints that may seriously interfere with quality of life, which can be defined as the physical and psychosocial situation of an individual, and the individual's personal appreciation of her situation and perspectives in life. Moreover, estrogen deficiency may be associated with chronic diseases, such as osteoporosis, coronary heart disease (CHD) and dementia, which all substantially interfere with life expectancy and well-being.

Of course, the menopausal transition is not only an endocrinological phenomenon. It often coincides with other life events or problems, such as illnesses, deaths of friends or relatives, children leaving the family home, parents being old and in need of care and attention, (early) retirement or unemployment, and marital problems or divorce. Coping mechanisms to deal with these life events may easily fail if someone is also experiencing one or more climacteric symptoms.[3-5]

Since estrogen deficiency plays a central role in climacteric problems, estrogen therapy is likely a rational treatment for women experiencing these symptoms and who are at risk for the associated chronic diseases. This review focuses on menopause as a factor interfering with, and discusses postmenopausal hormone therapy (PHT) as one option for improving, women's health and quality of life.

1. Definitions

Since there are considerable inconsistencies in the terminology used by different authors, the definitions of some frequently used terms are given.

- Menopause: the time of last vaginal bleeding induced by the influence of ovarian hormones on the endometrium. Natural menopause can only be established in retrospect, after 12 consecutive months of amenorrhoea. The median age of menopause is 51 years. In the US, the term menopause is also used with reference to the postmenopausal period.
- Postmenopause: the stage of life after the menopause.
- Climacteric: the years of perimenopausal transition in which definitive physical changes linked to ovarian aging take place in a woman's body. These physical changes are often accompanied by changes in family and social environment that may have a profound influence on psychosocial functioning.
- PHT: medication with estrogens or a combination of estrogens and progestogens (including perimenopausal use of oral contraceptives) for the treatment of climacteric symptoms or for the prevention of chronic diseases related to estrogen deficiency. PHT is a modern description of what was traditionally referred to as hormone replacement therapy (HRT).

Table I. Climacteric symptoms according to Greene[11]

Psychological		Somatic	Vasomotor	Sexual
anxiety	depression			
Heart beating quickly or strongly	Feeling tired or lacking energy	Feeling dizzy or faint	Hot flushes	Loss of interest in sex
Feeling tense or nervous	Loss of interest in most things	Pressure or tightness in head or body	Sweating at night	
Difficulty in sleeping	Feeling unhappy or depressed	Parts of body feel numb or tingling		
Excitability	Crying spells	Headaches		
Panic attacks	Irritability	Muscle and joint pains		
Difficulty in concentrating		Loss of feeling in hands or feet		
		Breathing difficulties		

2. Climacteric Symptoms

Typical problems related to the menopausal transition are irregular and heavy bleeding, and vasomotor and urogenital symptoms. Each of these problems may seriously interfere with quality of life for climacteric women.

2.1 Vaginal Bleeding

Most women in their forties experience menstrual-cycle changes, sometimes resulting in irregular and heavy menstruation.[6] Although hormonal disturbances are often the explanation for perimenopausal bleeding problems, organic causes should be ruled out. Hormonal treatment, either with progestogens only or with oral contraceptives, is the most common intervention in women with irregular bleeding problems.[7,8] Common adverse effects of oral contraceptives are weight gain, abdominal discomfort, spotting and breast tenderness. These effects usually disappear within 3 months in most patients.

2.2 Vasomotor Symptoms

Vasomotor symptoms, such as flushes and sweats, especially during the night, vary strongly in frequency and severity, and also differ within and between various societies.[9] The severity of vasomotor complaints is related to overall reduced well-being.[10] The most severe symptoms occur between 3 months and 3 years after the last menstrual bleed. Symptoms are already present in about 40% of regularly menstruating women aged ≥40 years, but become more severe and frequent if menstrual cycles become irregular. Around menopause, about 85% of women experience flushes and one-third describe them as severe.[10] Many women aged >60 years may still experience vasomotor symptoms. Since flushes often interfere with normal sleep, insomnia plays a major role in the development of many atypical complaints, which are well described by Greene[11] (table I). Besides the Greene Climacteric Scale, several other questionnaires have been developed and validated to assess climacteric symptoms. These questionnaires include the Women's Health Questionnaire, the Menopausal Symptom List, the Menopausal Rating Scale and the Utian Menopause Quality of Life Score.[12]

2.3 Urogenital Symptoms

Urogenital complaints (table II) such as dysuria, urgency, urge incontinence, urinary frequency and nocturia all increase with age, and almost 50% of women relate the onset of such problems to the menopause.[10] Estrogens affect the amount of collagen in skin and urogenital tissue, and the contractile response of urethral smooth muscle, and thereby contribute to female urogenital condition and performance.[13] Symptoms associated with urogenital atrophy often impair a woman's personal and rela-

Table II. Symptoms related to urogenital atrophy

Vaginal symptoms	Urological symptoms
Irritation, vaginal dryness	Dysuria
Vaginal discharge and infection	Frequency
Vulvovaginal itching	Nocturia
Dyspareunia	Urgency
Postcoital bleeding	Incontinence
Uterine prolapse	Recurrent urinary tract infection

tional happiness. Vaginal dryness and irritation may lead to dyspareunia and, thereby, to a problematic sexual relationship, whereas micturitional complaints such as frequency and incontinence may impair a woman's social freedom.

3. Chronic Disorders Associated with Menopause

With increasing age, men and women are confronted with a higher risk of chronic diseases, such as osteoporosis, cardiovascular disease and dementia. In addition to age, menopause has been suggested as an independent risk factor for such chronic diseases in women, which can seriously impair quality of life.

3.1 Osteoporosis

After age 30 years, aging in men and women is associated with bone loss.[14,15] Anovulation, amenorrhoea in athletes, premature ovarian failure, Turner's syndrome, early surgical menopause and physiological menopause, are all conditions associated with bone loss, and indicate that estrogen deficiency is an additional, independent risk factor for osteoporosis in women.[14-16] In the perimenopausal years, bone loss is accelerated, resulting in destruction of bone architecture and an increased risk of bone fractures.[16] At age 50 years, a (White) woman faces risks of 15% for forearm fracture, 30% for vertebral fracture and 15% for hip fracture, during the rest of her life;[16] the lifetime risk of at least one osteoporotic fracture is 40%.[16] Genetic predisposition, calcium intake, smoking, and physical activity, are important modulators of this risk, besides factors such as long-term oligomenorrhoea or amenorrhoea, low body mass, hyperthyroidism, hyperparathyroidism and long-term corticosteroid use.[14-16]

Osteoporosis affects many people. In the US, 13–18% of postmenopausal White women have osteoporosis and about 20% of hospital beds are occupied because of hip fractures.[14,15,17] Hip fracture can result in 1-year mortality rates of 10–25% and up to 25% of patients with hip fracture may require long-term nursing-home care.[17,18] Only one-third of patients will fully regain their prefracture level of independence. Basic activities of daily living, such as walking independently, remain impaired in about 50% of hip-fracture patients. Vertebral fractures also cause considerable complications, such as back pain, height loss and kyphosis, which in turn may limit activities such as bending and reaching. Thus, together with cosmetic adverse effects, these complications may reduce feelings of self-esteem and interfere with quality of life.[17]

3.2 Cardiovascular Disease

The main cause of death in women living in developed countries is vascular disease related to atherosclerosis.[19,20] Before menopause, women have a much lower risk of developing CHD than age-matched men. Once women pass through the menopause, it takes about 6–10 years for the CHD rate to match that of men.[21] Many recognised CHD risk factors may be modified unfavourably by the menopause and, therefore, may contribute to the menopause-related increase in CHD prevalence[22] (table III). The lifetime risk of CHD for women aged 40 years is 30%.[23] About 75% of women aged >65 years who develop CHD will not directly die from the disease; however, half of these women will be incapacitated and will have impaired quality of life.

Stroke affects 5% of the population aged >65 years.[24,25] The extended hospitalisation that such patients require during recovery makes the economic impact of stroke one of the most significant in medicine. As a consequence of this incapacitating disease, patient quality of life is usually strongly affected.

3.3 Dementia

Many cognitive functions decline with aging, with the extent and pattern of decline varying according to individual characteristics and the type of function being examined.[26,27] Although it has long been suggested that estrogen deficiency may cause memory loss after menopause, this was not supported by data from the Rancho Bernardo Study.[28] Conversely, other studies have demonstrated improvements in specific cognitive functions, such as verbal memory, during estrogen therapy, and therefore suggest the involvement of estrogen deficiency in the pathogenesis of dementia in postmenopausal women.[29-32]

Table III. Cardiovascular risk factors and postmenopausal hormone therapy (PHT)

Observational studies			Mechanisms to explain observational studies			Randomised controlled trials	
clinical endpoint	effect of menopause	effect of oral PHT	surrogate endpoint	effect of menopause	effect of oral PHT	clinical endpoint	effect of oral PHT
CHD	↑	↓	Total cholesterol	↑	↓	CHD	±
CHD mortality	↑	↓	HDL-cholesterol	↓	↑	CHD mortality	±
			LDL-cholesterol	↑	↓		
Stroke	±	↑ or ↓ (depends on dosage)	Triglycerides	↑	↑	Stroke	↑
Stroke mortality	±	±	Lp(a)	↑	↓	Stroke mortality	±
			Postprandial triglycerides	↑	±		
VTE	±	↑	Homocysteine	↑	↓	VTE	↑
VTE mortality	±	±	Insulin resistance	↑	↓	VTE mortality	±
			Nitric oxide	↓	↑		
			Endothelin-1	↑	↓		
			Fibrinogen	↑	↓		
			Factor VII	↑	↑ or ↓		
			PAI-1	↑	↓		
			APC resistance	?	↑		
			CRP	?	↑		
			Blood pressure	↑	± or ↓		

APC = activated protein C; **CHD** = coronary heart disease; **CRP** = C-reactive protein; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **Lp(a)** = lipoprotein (a); **PAI-1** = plasminogen activator inhibitor-1; **VTE** = venous thromboembolism; ↑ indicates increase; ± indicates no change; ↓ indicates decrease; **?** indicates unknown.

3.4 Diabetes Mellitus

Already mildly elevated glucose levels are a risk factor for cardiovascular disease.[33] Furthermore, diabetes mellitus is strongly related to obesity and eliminating central obesity would markedly reduce diabetes prevalence. Although a relationship between glucose metabolism and estrogen levels has been suggested, no evidence exists that menopause is a risk factor for diabetes.[19,22]

3.5 Obesity

Obesity is an important, independent cardiovascular risk factor,[34] and approximately 33% of US adults are overweight.[35] Weight gain is associated with an atherogenic lipid profile, and increased blood glucose levels, insulin resistance, uric acid, blood pressure and left ventricular size. Generally, as age increases, so does bodyweight.[35] Exercise and diet programmes are probably the best way to reduce obesity and, thereby, cardiovascular risk. Exercise has multiple benefits, including reduced appetite, preserved lean body mass, and improved mood and self-image.

3.6 Skin Aging

The hypoestrogenism that occurs after the menopause leads to a profound deterioration in the skin.[13,36,37] However, estrogen receptors have been identified in the skin (their concentration varies in different parts of the body), and estrogen administration improves the skin in more ways than one: collagen content and quality is improved, skin thickness is increased and vascularisation is enhanced. The extracellular matrix responsible for the tone and appearance of skin is also improved. Moreover, it is not just the skin that improves but also skin appendages such as hair. Although skin aging is not totally estrogen dependent, since the effects of age and the external environment also play important roles, estrogen therapy reverses the deleterious effects of estrogen deprivation on the skin, which is thus yet another organ that benefits from PHT.[37]

4. Counselling

The primary goals of counselling the climacteric woman who seeks help are to clarify her symptoms (table I) and risks (personal and family history). Quality-of-life assessments can be made using modern questionnaires (see section 2.2), and additional physical examination and laboratory studies may be indicated. To estimate the impact of a woman's symptoms on quality of life and the usefulness of starting a treatment, her fears and expectations regarding the menopause, and the perceived benefits and risks of the various treatment options, should be discussed. Besides reviewing treatment modalities, attention should be given to lifestyle recommendations, such as reduction of bodyweight or prevention of weight gain, cessation of smoking, modification of alcohol intake, proper nutrition, regular exercise and sex education.[38]

5. Postmenopausal Hormone Therapy (PHT)

Both the short-term and long-term consequences of estrogen deficiency can be managed with estrogen therapy. The definite and potential benefits of PHT are summarised in table IV. Most of the data presented in this section are based on studies investigating the oral route of PHT administration. The preventive effects of PHT may protect some women from disabling and life-threatening diseases and, for many years, attention was given to the preventive effects of estrogen against osteoporosis, CHD and dementia. Most observational studies were very positive in this respect; however, substantial criticism of these studies was based on their lack of a randomised, controlled design.

5.1 Climacteric Symptoms

Continuous administration of low doses of estrogen is the first-choice treatment for women experiencing vasomotor and urogenital symptoms.[39-44] By eliminating flushes and nightly sweats within several weeks of starting treatment, sleep disturbances and other complaints secondary to insomnia will also usually disappear.[10,39] Atypical complaints, such as agitation, nervousness, mood changes, anxiety, irritability, loss of memory and concentration, crying spells, tiredness, loss of sexual desire, depression, headaches, and joint or muscles pains, may be improved by estrogen therapy, especially in the presence of vasomotor symp-

Table IV. Benefits and risks associated with postmenopausal hormone therapy (PHT)

Benefits	Risks
Definite	**Definite**
Climacteric symptoms	Endometrial cancer
>70–80% decrease	8–10 times increased risk with unopposed estrogens for ≥10 years
Osteoporosis	excess risk of 46 cases/100 000 women-years
25–50% decrease in fracture risk	combined PHT: no excess risk
absolute reduction of 172 hip fractures/100 000	Venous thromboembolism
women-years	2.7 times increased risk
Colorectal cancer	primary prevention: excess risk of 20 cases/100 000 women-years
35% decreased risk	secondary prevention: excess risk of 390 cases/100 000 women-years
absolute reduction of 60 cases/100 000 women-	Stroke
years	23–41% increased risk
Uncertain	excess risk of 80 cases/100 000 women-years
Coronary heart disease	Breast cancer
primary prevention uncertain	25–35% increased risk with PHT use for >5 years
	excess risk at 5 years of 200 cases/100 000 women
	excess risk at 10 years of 600 cases/100 000 women
	excess risk at 15 years of 1200 cases/100 000 women
	Gallbladder disease
	38% increased risk
	excess risk of 540 cases/100 000 women-years
	Probable
	Coronary heart disease
	primary prevention uncertain

toms.[10,39] Indeed, significant improvements in atypical climacteric complaints are more likely to be attained in women with rather than those without flushes and night sweats.[10,39]

In deciding whether or not to start PHT to relieve climacteric complaints, a history focusing on the severity of vasomotor symptoms is essential.[10] Complaints associated with urogenital atrophy can often be effectively treated with systemic and local (vaginal) administration of estradiol or estriol succinate.[43,44] Improvement in one or more climacteric complaints enhances quality of life, as demonstrated in several studies using validated quality-of-life questionnaires.[45-48] Interestingly, however, in the recently published Women's Health Initiative (WHI) trial, there were no general, clinically meaningful improvements in variables related to quality of life.[49] Only in a subgroup of women aged 50–54 years, and with moderate-to-severe vasomotor symptoms at baseline, did PHT improve these symptoms and produce a small benefit in terms of sleep disturbances. However, the WHI was not designed to look specifically at symptom benefit and quality of life. Fewer than 3% of the more than 16 000 participants had vasomotor symptoms.[49] Overall, therefore, for women without menopausal symptoms and with no increased risk of osteoporosis, there is no indication for, or benefit to be gained from, PHT.

5.2 Osteoporosis

Despite the large number of studies demonstrating beneficial effects for PHT on bone mineral density, even at low dosages, the number of randomised, placebo-controlled fracture trials is limited. In a recent meta-analysis of randomised controlled trials of PHT, an overall reduction in nonvertebral fractures was found in women using PHT compared with non-users (relative risk [RR] 0.73; 95% CI 0.56, 0.94; p = 0.02).[50] For hip and wrist fractures alone, the effectiveness of PHT appeared more marked (RR 0.60; 95% CI 0.40, 0.91; p = 0.02). These observations were recently confirmed by the

WHI trial,[51] which showed a 34% reduction in the incidence of osteoporotic hip fractures (RR 0.66).

5.3 Cardiovascular Disease

Until recently, no randomised controlled trials were available to establish the role of PHT in preventing CHD. Nevertheless, the overwhelming number of studies showing beneficial effects for PHT on surrogate endpoints, such as lipids, lipoproteins, homocysteine and endothelial function, plus animal studies and *in vitro* research, convinced many clinicians to believe in cardiovascular protection for estrogens.[52-62] Unlike epidemiological and surrogate-endpoint studies, however, almost all of which indicated a cardiovascular protective benefit for PHT, recent randomised controlled trials reported no such benefit[51,63-67] (table III). According to latest results from the WHI trial, long-term combined estrogen-progestogen therapy had no beneficial effect on CHD risk (RR 1.29) in postmenopausal women of mean age 63 years.[51] Also, the risk of ischaemic stroke was slightly increased (RR 1.44).[68] Therefore, prevention of cardiovascular disease is no longer considered an indication for initiating or continuing PHT.[51,68] Presently, the debate is ongoing about whether or not the WHI results also apply to peri- and early postmenopausal women.[69-72]

5.4 Alzheimer's Disease

Estrogens have been reported to exert neuromodulatory and neuroprotective effects,[73,74] and randomised controlled trials concerning the prevention of Alzheimer's disease are still ongoing. Recently, however, the WHI Memory Study[75,76] reported that women starting PHT at very old age are not protected against Alzheimer's disease or declining cognitive function. Since this study does not represent the population actually using PHT, it has limited clinical applicability. Conversely, results from a meta-analysis of observational studies are promising: a lower incidence of Alzheimer's disease was noted in women after long-term PHT started at an early menopausal rather than very old age.[77] Thus, although available evidence suggests that estrogen therapy for the prevention of chronic diseases involving estrogen deficiency should start early in a climacteric woman's life and be given for many years, probably lifelong, certain contradictory results suggest that PHT should not be initiated for the prevention of dementia.

5.5 Diabetes Mellitus

Oral estrogen therapy appears not to influence glucose metabolism, although both standard and low-dose therapy may slightly improve insulin sensitivity. On the other hand, transdermal estrogen therapy may have some advantage over oral treatment, since triglycerides and free-fatty acids are not affected by transdermal administration but are increased during oral therapy.[78-80]

5.6 Obesity

In general, PHT does not influence bodyweight. Individual weight increases may occur, but are usually associated with fluid retention. In elderly women, weight generally increases slightly but is not affected by PHT.[56]

5.7 Colorectal Cancer

For several years, large observational studies have indicated that PHT may have a protective effect against colorectal cancer. In the Nurses' Health Study, for example, the risk of colorectal cancer was reduced by 35% in women currently using PHT and by 16% in women who had previously used PHT.[81] These findings were confirmed by meta-analyses,[82,83] and by the recently published WHI trial,[51] which reported a relative risk of colorectal cancer of 0.63 for PHT users. Several mechanisms, such as estrogen-induced modulation of the vitamin D endocrine system, have been suggested to explain these observations.[84,85]

6. Adverse Effects of PHT

Estrogen administration may also have negative effects, including vaginal bleeding, breast tenderness, fluid retention, nausea and bloating. Within a few months, these adverse effects usually diminish but, if not, lowering the estrogen dosage is an effective strategy.[86,87] Non-oral routes of administration may give specific adverse effects, such as irritation of the skin or nasal mucosa. In non-hysterectomised women, addition of a progestogen in adequate dos-

age and duration is mandatory to prevent the increased risks of endometrial hyperplasia and carcinoma associated with unopposed estrogen use.[88,89] However, progestogens may also have adverse effects, such as vaginal bleeding, breast tenderness and mood changes.[90] For adverse effects occurring specifically during progestogen administration, decreasing the frequency of progestogen use to a 2- or 3-monthly regimen may be an option.[91] However, this may impair endometrial protection.[92] Changing from systemic to local (intrauterine) administration of the progestogen may be an attractive alternative.[93] When withdrawal bleeding induced by sequential combined estrogen-progestogen regimens is limiting a woman's satisfaction with PHT, changing to a continuous combined regimen can produce a significant improvement.[94] In general, continuous combined PHT should be started in women with amenorrhoea for >1 year (figure 1). The definite and probable risks associated with PHT use in healthy women are summarised in table IV.

6.1 Endometrial Disease

Unopposed estrogen use by non-hysterectomised women is associated with an increased risk of endometrial abnormalities such as hyperplasia and carcinoma.[88] The risk increases with the dosage and duration of estrogen administration. After 10 years of unopposed estrogen use, the relative risk of endometrial cancer is around 10.[88] Also, low estrogen dosages and relatively weak estrogens, such as estriol succinate, increase the risk.[88,89] The standard way of opposing the risk is to combine an estrogen with progestogen in an adequate dosage and duration.[89,90] Since long-term, sequentially combined PHT use has been suggested to increase endometrial cancer risk if the progestogen is administered <12–14 days per month, the recommended duration should be at least 12, but preferably 14, days per month[89] (see figure 2). The daily addition of a progestogen to estrogen has even been reported to reduce the risk of endometrial cancer by about 40–60%.[95] At the moment, however, some debate is going on as to whether or not there is an indication for combining estrogen with a progestogen, since absolute risks for unopposed estrogen therapy are rather low and progestogens can induce several adverse effects.[90,96,97]

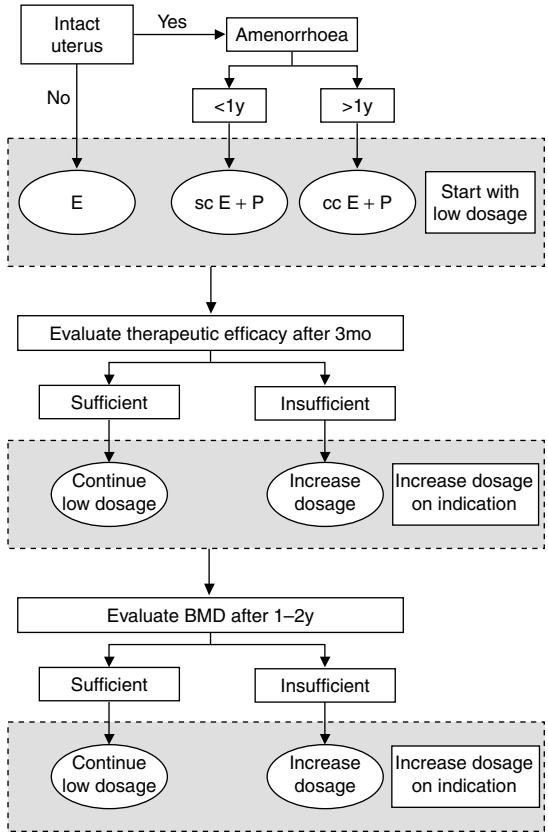

Fig. 1. Guide for postmenopausal hormone therapy. **BMD** = bone mineral density; **cc** = continuously combined; **E** = estrogen; **mo** = months; **P** = progestogen; **sc** = sequentially combined.

6.2 Thromboembolic Disease

During PHT, the risk of thromboembolic disease is increased about 2–4 times; this means an additional risk of about one case per 5000 women-years of PHT use.[98] This increased risk is concentrated in the first 2 years after starting PHT. From scarce data available, it was suggested that this increased risk was especially related to the oral use of hormones, and that transdermal administration was possibly associated with a smaller increase in risk.[98,99] This was confirmed by a study that found substantial attenuation of increased resistance to activated protein C, a major risk factor for venous thromboembolism, by transdermal versus oral estrogen therapy.[100]

6.3 Breast Cancer

The risk of breast cancer increases by a factor of 1.023 for each year of PHT use.[101] The relative risk is about 1.25 after 5 years of PHT use in healthy women.[51,101] Absolute additional risks are estimated to be in the order of 2 per 1000 women after 5 years, 6 per 1000 women after 10 years and 12 per 1000 women after 15 years of PHT use.[101] Additional risks disappear within 5 years of treatment discontinuation.[101]

Little is known about PHT and recurrence risk for breast cancer in women with a history, or at high risk, of breast cancer. However, in contrast with the current practice of not prescribing PHT to such women, data from observational studies are reassuring.[102,103] No excess recurrence risk was observed in women treated with continuous combined PHT, neither was it proven that in the presence of other risk factors (e.g. a positive family history), PHT further increased the recurrence risk.[102]

Recently, results from the Million Women Study (MWS) were published.[104] The difference in breast cancer risk reported in this large, observational study compared with that in the randomised, controlled WHI trial,[51] together with the fact that several MWS observations appear to be biologically implausible, justify the conclusion that the MWS merely confirms current knowledge that long-term PHT slightly increases breast-cancer risk.[105] Therefore, current opinions and guidelines should not be changed.[105]

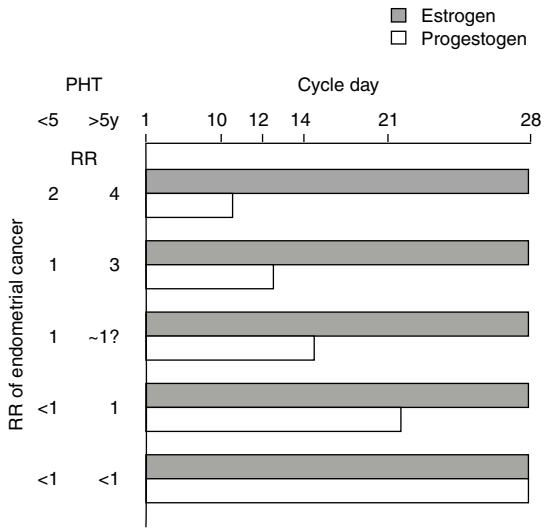

Fig. 2. Relationship between the relative risk (RR) of endometrial cancer (i.e. risk relative to women not receiving postmenopausal hormone therapy [PHT]), duration of PHT (i.e. less or more than 5 years), and duration of progestogen use per cycle.

6.4 Ovarian Cancer

The risk of death from ovarian cancer is more than doubled in women who have used estrogen therapy for ≥10 years compared with women who have never used estrogen therapy (annual age-adjusted death rate: 64.4 versus 26.4 per 100 000 women).[106] In an updated, collaborative re-analysis of European case-control studies, an increased risk of ovarian cancer for current or previous users of PHT, versus women who had never used PHT, was also found (odds ratio 1.28; 95% CI 1.05, 1.56).[107]

6.5 Coronary Heart Disease

Recent, randomised controlled trials suggest that early after starting PHT, the risk of CHD increases both in healthy women[51] and those with established coronary disease.[63] The debate is ongoing about whether or not the WHI trial is representative for primary prevention, since the trial was performed in a rather old population (mean age 63 years), including women with one or more risk factors for CHD. Nevertheless, the potential for excess CHD risk early in the course of PHT must be considered, especially when starting PHT in older women with an already elevated risk of CHD.[71]

6.6 Gallbladder Disease

Gallbladder disease has been reported as another risk associated with PHT use.[108] The relative risk of biliary tract surgery is increased by 38% in women receiving PHT, meaning that one additional woman requires biliary tract surgery for every 185 women treated with PHT.[108] This may be due to an estrogen-induced increase in biliary cholesterol saturation.[109]

7. Adherence to PHT

Despite significant improvements that PHT may produce in quality of life, either in the short term by relieving symptoms or in the long term by preventing chronic diseases, adherence to this type of treat-

Table V. Strategies to improve patient adherence to postmenopausal hormone therapy (PHT)

Recognise that menopause causes permanent estrogen deficiency
Understand system, organ and tissue consequences of estrogen deficiency
Appraise benefits and risks of PHT
Educate patients about the nature and consequences of permanent estrogen deficiency
Implement an acceptable course of action
Promptly evaluate the real and perceived consequences of intervention
Re-evaluate the real and perceived benefits and disadvantages/ risks of intervention at regular intervals
Engage interactive discussions; provide printed information
Be aware of, and discuss with patients, information and misinformation through the media, various health advocacy groups and well-meaning friends

ment is low.[110-112] Several factors contribute to such low adherence: for example, adverse effects, both irregular and regular bleeding, and fear of cancer.[41] Therefore, periodic reassessment, reinforcement and revision of the efficacy and safety of the PHT regimen used is advocated[38,41,113] (see table V).

8. Individualised Treatment

Most of the large observational studies and randomised controlled trials of PHT have used orally administered estrogens, either unopposed or combined with an orally administered progestogen.[40] Studies from the US commonly used conjugated equine estrogens and medroxyprogesterone, whereas in European countries, various PHT formulations are available, differing in type of estrogen and progestogen, dosage, and route and frequency of administration.[44,86,87,114,115] This expands the range of opportunities for doctors to meet patients' needs and improve quality of life.

It is primarily a matter of personal opinion and experience as to which formulation a doctor will choose for an individual woman but, in general, the authors' strategy is to start with a low-dose preparation given via an administration route (oral, transdermal, intranasal, etc.) that the woman prefers. If indicated because of unsatisfactory symptom relief or the need to prevent bone resorption, the estrogen dosage can be increased over time. Whether or not to combine the estrogen with a progestogen, and to do this in a sequential or continuous manner, depends primarily on the presence of an intact uterus and the time since the last menstruation, respectively (see figure 1).

Low-dosage PHT has the advantage over higher-dosage PHT of being associated with fewer adverse effects (e.g. fluid retention, breast tenderness, and withdrawal and breakthrough bleeds).[86,87,116] This is of great importance in terms of unnecessary discontinuation of hormone treatment. Low-dosage PHT has also been shown to be effective in many women for relieving symptoms and preventing bone loss.[86,87,116,117] For women who might temporarily need a higher PHT dosage, it is preferable to titrate towards the individual optimal dosage (see figure 1).

Androgen therapy is a new treatment modality for climacteric women. Symptoms of relative androgen deficiency (e.g. lack of energy and motivation, and disorders of mood, sleep and/or sexual arousal) that persist during adequate estrogen therapy can substantially impair well-being.[118,119] Although some studies indicate that significant improvements can be achieved with androgen therapy, there is currently no consensus on this topic.[118] Furthermore, in many countries, there are no marketed formulations available for the treatment of women.

In the process of individualising therapeutic decisions, periodic evaluation of treatment efficacy and tolerability, and of patient satisfaction with treatment, is mandatory.[38,113]

9. Alternatives to PHT

Since the implications of hormone use may vary depending on an individual's situation, counselling a climacteric woman should address the possibility of changing to an alternative treatment or a combination of alternatives (table VI).

Table VI. Alternatives to estrogen-based postmenopausal hormone therapy

Climacteric symptom relief	Osteoporosis prevention
Tibolone	Tibolone
Phytoestrogens	Calcium, vitamin D, exercise
Clonidine	Selective estrogen receptor
Selective serotonin reuptake	modulators
inhibitors	Bisphosphonates

An alternative to conventional PHT, but in many ways mimicking continuous combined estrogen-progestogen preparations, is tibolone.[120,121] Its main metabolites have estrogenic (3α-OH-tibolone and 3β-OH-tibolone), and progestogenic and androgenic (Δ4-isomer) activities. As with conventional continuous combined PHT, tibolone improves menopausal symptoms, prevents bone resorption and induces amenorrhoea. However, it may cause less breast tenderness[122] and improve several aspects of sexual well-being;[123] the latter may well be related to the mild androgenic properties of tibolone. Furthermore, tibolone has been reported to exert its tissue-specific effects by modulating local tissue enzymes; it is therefore classified as a selective tissue-estrogen activity regulator.[124]

As an alternative to PHT, vasomotor symptoms can be treated, although usually less effectively, with, for example, clonidine.[125] Recent studies in patients with breast cancer have shown that serotonin reuptake inhibitors (e.g. fluoxetine, venlafaxine) are also effective drugs for relieving vasomotor symptoms.[126,127] Isoflavone-containing preparations may also provide some relief.[128]

For the prevention of osteoporotic fractures, selective estrogen receptor modulators (SERMs) and bisphosphonates are excellent alternatives to PHT.[129] The second-generation SERM raloxifene has several other characteristics besides bone preservation that may also produce quality-of-life benefits in menopausal women.[130] For example, raloxifene does not stimulate the endometrium and, thereby, induces amenorrhoea.[130] It reduces the risk of breast cancer, especially cancer with estrogen receptor expression.[131] Furthermore, raloxifene has favourable effects on several cardiovascular surrogate endpoints and, in elderly osteoporotic women with high cardiovascular risk, it was found to reduce CHD risk.[61,132] However, raloxifene does not improve vasomotor symptoms and, thus, its applicability is restricted mainly to elderly women without flushes. Bisphosphonates effectively reduce the risks of new and recurrent hip and lumbar vertebral fractures.[129,133] Adverse effects are mainly restricted to the gastrointestinal tract.[133]

For the prevention of cardiovascular disease, a broad spectrum of drugs is available. Depending on a patient's risk profile, cardiologists can choose between interventions that improve, for example, haemostasis (e.g. aspirin [acetylsalicylate acid]), lipids (e.g. statins), homocysteine (folic acid) and blood pressure (e.g. diuretics or β-adrenergic antagonists).

10. Conclusions

Quality of life is often compromised in climacteric and postmenopausal women. Many factors, including psychosocial variables, may interfere with the happiness of such women. The hormonal changes during the menopausal transition, finally resulting in estrogen deficiency, usually, but not exclusively, play a pivotal role in this respect. PHT is the treatment of first choice to alleviate symptoms of estrogen deficiency. Besides effectively relieving climacteric symptoms and complaints, PHT can also protect against chronic diseases (e.g. osteoporosis and colorectal cancer) that may seriously interfere with quality of life. The protective role of hormone therapy in relation to CHD and Alzheimer's disease remains contentious.[71,72,75-77]

Guidelines and statements from different societies have been published to support clinicians in the care of menopausal women.[134-138] At present, many hormonal therapies are available, varying in type and dosage of hormone, and route and duration of administration. Furthermore, the number of alternatives to treat climacteric symptoms, and/or to prevent chronic diseases, has also increased. Therefore, doctors involved in the care of climacteric women in the 21st century are much more able to meet a woman's specific needs and improve quality of life. Individualised approaches to menopausal care are possible, and indeed mandatory, to achieve optimal therapeutic results.

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