Pergamon

0960-0760(95)00047-X

J. Steroid Biochem. Molec. Biol. Vol. 53, No. 1–6, pp. 205–208, 1995

0960-0760/95 $9.50 + 0.00

Benefits and Risks of Hormone Replacement Therapy (HRT)

M. Breckwoldt,* C. Keck and U. Karck

Department of Obstetrics and Gynecology, Division of Clinical Endocrinology, Reproductive Medicine and Andrology, University of Freiburg, 79106 Freiburg, Germany

In western countries more than 30% of the female population are postmenopausal. Approximately 30% of postmenopausal women suffer from clinical symptoms of the climacteric such as vasomotor symptoms, associated with hot flushes, night sweat, insomnia and depressive mood. Sufficient hormonal replacement therapy (HRT) will abolish specific menopausal symptoms in over 90% of patients, unspecific symptoms such as headache respond to placebo and HRT equally well. The question of cancer risk related to HRT will be addressed in this review. In combination with progestins, estrogens are obviously protective regarding ovarian and endometrial cancer. The association between HRT and breast cancer risk is presently unclear. Epidemiological data available so far do not provide compelling evidence as to a cause and effect relationship between HRT and breast cancer risk. There seems to be an overall trend towards a slightly increased risk with increasing duration of HRT use. Guidelines for HRT use in women with a history of endometrial and breast cancer are provided in this article.

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INTRODUCTION

In this article some general aspects on benefits and risks of HRT will be discussed excluding effects on bone metabolism and on the cardiovascular system. The complex of vasomotor symptoms, the effects on the central nervous system and finally the question of cancer risk associated with HRT will be considered.

By definition menopause means the last menstrual period in a woman's life depending on ovarian function. The life span of the ovary is determined by genetic factors and by the number of primordial follicles. During fetal life the ovaries contain about 7 million primordial follicles. Already before birth this number begins to decline rapidly and even during childhood, when the ovaries are endocrinologically quiescent, regression of primordial follicles continues. Absence or defects of an X-chromosome are associated with an accelerated regression resulting in premature menopause.

Normally, menopause can be expected around the age of 52. Applied to western countries this means that more than 30% of the female population are postmenopausal. Considering the fact that life expectancy of the female population has continuously increased during this century, it becomes evident that we are facing an increasing socio-economic and medical challenge, since morbidity and mortality rates are age-dependent phenomena.

Due to continuous regression the ovary becomes atrophic being unable to mature follicles and consequently to secrete estradiol. Only minor amounts of androstendione are produced and secreted by interstitial ovarian cells. Androstendione can be aromatized by peripheral tissue to estrone, only a small amount of which can be further converted to estradiol. Compared to the premenopausal period the ratio of estradiol to estrone is changed after the menopause in favour of estrone. The decreased production of estradiol and progesterone results in disinhibition of hypothalamic and pituitary function. A yet undefined pulse generator governs the GnRH-producing neurons which are concentrated in the arcuate nucleus and stimulate the anterior pituitary to secrete high amounts of FSH and LH into the circulation. In addition the atrophic ovary is unable to produce inhibin which is known to suppress pituitary FSH secretion. Therefore the increment in FSH-secretion after cessation of ovarian function is even larger than that of LH, resulting in higher peripheral concentrations of FSH. The menopausal status can

Proceedings of the IX International Congress on Hormonal Steroids, Dallas, Texas, U.S.A., 24–29 September 1994.
*Correspondence to M. Breckwoldt.

be defined as hypergonadotropic hypogonadism due to primary ovarian failure.

In about 35% of all women passing the menopause climateric symptoms are absent; in about another 35% clinical symptoms of the climateric are recognized but seem tolerable. In about 30% the clinical symptomatology impairs wellbeing and medical advice is asked for. Climateric symptoms can be related to the autonomous nervous system causing vasomotor symptoms, furthermore, estrogen deficiency can be associated with psychological symptoms such as depressed mood and irritability. The urogenital system is also affected by estrogen deficiency causing atrophy of the target organs. In the long run cardiovascular risk and risk of osteoporosis have to be considered.

Vasomotor-symptoms may persist for longer than 5 years in 25% of climacteric women and may be even lifelong in a small minority. Hot flushes are conventionally considered as a characteristic clinical manifestation of the climateric. One of the main problems in studying hot flushes is their extreme variability. They can already occur in the perimenopausal phase in women who are still menstruating and may even be very pronounced at that stage. The intensity and frequency of flushing frequently varies in the same women, flush episodes may occur as frequently at 50 times per 24 h, especially during nighttime. Since each flush is followed by perspiration one can easily imagine the impairment of well-being. Thus insomnia is a natural consequence. Hot flushes can be detected by monitoring skin temperature and by studying the blood flow in peripheral organs. Ginsburg *et al.* [1] demonstrated a rapid increase in blood flow and pulse rate during flush episodes. The pathophysiology of this phenomenon, however, is still unclear. Because of the assumed association between LH-pulses and flush episodes it was suggested that there is a link between central thermoregulation and the GnRH pulse generator that initiates episodic secretion of GnRH. Anatomically the thermoregulatory center and the GnRH-secreting neurons are closely linked. However, flush episodes also occur in 90% of women under treatment with GnRH-agonists to down-regulate FSH and LH secretion. In these women pulsatility of FSH and LH is completely blunted. Therefore hot flushes must be attributed to estrogen deficiency. In addition neurotransmitters such as noradrenalin, dopamine and endogenous opioids such as β-endorphin and encephalin have also been suggested to be involved in the pathophysiology.

However, none of the studies using specific agonists and antagonists to various transmitter substances or naloxon as an opiate antagonist provided convincing evidence to clarify the pathophysiology of vasomotor symptoms. Despite the fact that we are left with the message that the pathophysiology of hot flushes is unclear we have to accept that estrogen replacement will completely abolish this phenomenon in over 90% of the patients.

MENOPAUSE AND DEPRESSION

It is still an unsolved clinical problem as to if and how estrogens can be regarded as psychotropic agents [2]. In general, low peripheral estrogen levels are not associated with increased incidence of depression, however, a sudden decrease of estrogen concentrations can at least be partly responsible for depressive mood. This phenomenon is not uncommon in the postpartal period.

From epidemiological studies it is obvious that women between 45–50 years are more frequently affected by depressive symptoms than men. In a double blind cross over study design [3] it was demonstrated that estrogen replacement after ovariectomy resulted in a lower depression score than placebo. These findings are confirmed by others [4]. In a study by Best *et al.* [5] it was shown that ERT in postmenopausal women results in a significant reduction of anxiety and depression. Similar results were reported by Montgomery *et al.* [6].

On the other hand it has been argued that depressive mood during the climacteric period is secondary to hot flushes, night sweats and insommia [7].

Impairment of central serotonin function is thought to be responsible for depression [8]. Decrease in dopamine and noradrenalin concentrations in the brain are also believed to be involved in the pathogenesis of depression. Antidepressant agents act either as dopamine antagonists or as monoamino oxydase inhibitors leading to increased neurotransmitter levels. It has been proposed that estrogens can be considered as natural monoamino oxydase inhibitors.

From animal experiments it is further known that estrogens inhibit the activity of co-methyltransferase (COMT) leading to increased dopamine and noradrenaline levels. The link between estrogens and catecholamines can be explained by the formation of catecholestrogens. By 2-hydroxylation, estrogens can be converted to catecholestrogens which are preferentially metabolized by COMT. There is additional evidence from the work of Smith that steroids are able to modulate GABA-receptors by nongenomic binding to the β-subunit [9]. Furthermore glutamate-induced firing of neurons can be stimulated by estrogens [10].

In clinical studies it was shown that estrogens influence tryptophan release. A positive correlation between plasma estrogens and free plasma tryptophan in postmenopausal women being treated with estrogens has been demonstrated by Aylward [11]. However, a direct relationship between estrogen levels and depressed mood is not generally accepted.

Depression as a specific menopausal symptom has been questioned by many psychiatrists since endogenous depression cannot be cured by estrogen administration [12]. There is no conclusive evidence that

estrogen therapy improves depression over and above placebo effects [13]. Therefore depressive mood during the climacteric should be clearly distinguished from endogenous depression. It seems appropriate to use the term depressive mood or melancholia in order to characterize psychological impairment related to estrogen deficiency. The efficacy of HRT on various menopausal symptoms has been demonstrated in a double blind placebo controlled cross-over study by Coope [14]. Symptoms like hot flushes, insomnia, headache and melancholia were scored and monitored. From these data it becomes evident that specific menopausal symptoms respond well to HRT. Estrogens are clearly more effective than placebo, improvement of the symptoms is found in the order of 80–95%. Unspecific symptoms, such as headache, however, respond to placebo and estrogens equally well.

HRT AND CANCER

Endometrial cancer

During the mid 1970s epidemiological studies provided evidence that the use of estrogens was associated with an increased relative risk of endometrial cancer. The relative risk increased from 4.1 after 5 years of unopposed estrogen use to 11.6 after 10 years of estrogen intake. These figures were alarming. On the basis of these findings it was proposed and generally accepted to combine estrogens and progestins in order to reduce the risk of endometrial cancer. Indeed, the addition of a progestin for 12–14 days per cycle completely inhibits the development of cystic and adenomatosous hyperplasia and the relative risk for endometrial cancer drops to 0.2–0.4 indicating a significant protective effect. These results have been confirmed in a large number of epidemiological and clinical studies. Based on these findings even women with a history of endometrial cancer may be treated with estrogens in combination with progestins.

Breast cancer

The incidence of breast cancer steadily increases with age. Estrogens cannot be regarded as direct cancer-inducers, they may, however, stimulate tumor promotion provided the tumor is able to respond to estrogens. Breast cancer tissue may express estrogen and progesterone receptors. These tumors are obviously estrogen sensitive but seem less aggressive as compared to breast cancer tissue being estrogen receptor negative [15].

Under physiological conditions cell proliferation and differentiation is regulated by both promoter as well as suppressor genes. Carcinogenesis involves multiple steps, in particular, the presence of dysregulated expression of oncogenes and growth factors promoting uncontrolled cellular proliferation. Malignant transformation and uncontrolled cell growth requires genetic mutation. Mutations in the p53 suppressor gene and the breast cancer gene 1 are found in families with a high incidence in breast cancer. A proliferative cell is most susceptible to mutation during the phase of DNA synthesis. Since estrogens are growth promoting agents they may facilitate the risk of DNA damage. Women with early menarche and late first pregnancy are known to be at increased risk for breast cancer. The association between HRT and breast cancer risk is presently unclear. We are confronted with a large number of epidemiological studies: more than 20 case control studies and 4 cohort studies presenting inconsistent results with increased or decreased relative risks, or no effect at all [16]. Evaluation of these data by the means of meta-analysis is complicated by the facts that most of the major studies used unopposed estrogens, in some studies estrogens plus progestins were used, the number of cases and the length of treatment are variable. Despite of these variabilities Dupont and Page have plotted the data of 29 epidemiological studies related to this subject [17]. The inconsistency of the findings is quite evident. In summary it can be stated that the epidemiologic data available so far provide no compelling evidence as to a cause and effect relationship between HRT and breast cancer risk. The incidence of breast cancer steadily increases with age in contrast to endometrial cancer. Both malignancies are considered as estrogen sensitive tumors. While the incidence of endometrial cancer can be effectively reduced by HRT the incidence of breast cancer is obviously unaffected by exogenous sex steroids. From clinical studies it is known that early menarche and late menopause are associated with increased risk of developing breast cancer and that premature menopause correlates with a decreased risk. Pregnancies and long lactational periods are accepted to be protective against breast cancer.

Despite of these considerations the clinician is left with the available epidemiological data. Some of the recently published studies provide a significant overall trend towards an increased risk with increasing duration of HRT use with a RR of 1.5 after 20 years of treatment. Results from a cohort study in Sweden covering 23,000 women with a follow-up period of 5–7 years showed a slightly elevated RR of 1.1. After more than 9 years of estrogen use the RR increased to 1.7 [18]. This duration dependent increase seems plausible since HRT artificially prolongs the time interval of menarche to menopause.

Five years ago endometrial and breast cancer were considered as absolute contraindications for HRT. Today, however, women with a history of endometrial cancer may use estrogen/progestin combinations without concern [19]. In patients with breast cancer more detailed recommendations are needed. Patients with ER and PR negative tumors may be treated with HRT since the tumor tissue is unable to respond to sex steroids [20]. Patients with ER and PR positive breast cancer should receive antiestrogens for adjuvant

therapy to improve their prognosis. However, the RR for endometrial cancer may increase due to inherent estrogenic property of most antiestrogens. Therefore it seems advisable to combine antiestrogens with progestins [19].

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