Radiol Oncol 1996; 30: 210-3.

Advantages and disadvantages of hormone replacement therapy

Sonja Bebar and Marjetka Uršič-Vrščaj

Department of Gynecology, Institute of Oncology, Ljubljana, Slovenia

In the developed countries, more than 30 % of female population is in the postmenopusal period of their life. Approximately one third of these present with severe clinical menopausal symptoms, such as hot flushes, sleeplessness, night sweats, and depression. Many women search medical help. By means of hormone replacement therapy (HRT), these problems can be either completely eliminated or alleviated in 90 % of women. The suspected association between HRT and risk of carcinoma should not be ignored, however. While estrogens in combination with progestogens exert a protective effec against ovarian and endometrial carcinomas, a possible correlation between HRT and breast cancer has not been fully explained yet. Nevertheless, some published reports have indicated a slightly increased risk of breast cancer after a prolonged use of HRT.

Key words: estrogen; replacement therapy

Is menopause a pathological or physiological condition? In endocrinology, the cessation of ovarian function is the only situtation where replacement of lacking hormones is not a self-evident act.

W. Craesman

Menopause

By definition, menopause is the last menarche in woman's life, which means the end of her fertile period. In the developed countries it occurs at about 50 years of age. Since a healthy woman is expected to live for another 30 years, the postmenopausal period is relatively long.[1] Considering the fact that life expectancy of female population has been increasing steadily in this century, certain changes in morbidity and mortality can be expected in this population group.

The cessation of menstruation occurs due to ovarian disjunction. The duration of their activity is determined by genetic factors as well as by the number of primordial follicles. In the fertile period the ovaries comprise approximately 7 million follicles. Their number starts to decrease before birth and continues to do so even more rapidly after it. The process ends with atrophy of the ovaries which cease to produce estradiol, the most potent estrogen; only a minimal quantity of androstendione is being release instead. In the peripheral tissues, this can be converted into estrone through aromatization process, while a small quantity is converted into estradiol. With respect to the premenopausal period, in postmenopause the rate between estradiol and estrone changes in favour of estrone which is a weak estrogen. The diminished secretion of estradiol and progesterone lead to changes in hypothalamic and hypophyseal function. Uncontrollable release of high GnRH values stimulates the frontal part of hypophysis to FSH and LH secretion.

Correspondence to: Sonja Bebar, M. D., Department of Gynecology, Institute of Oncology, Zaloška 2, 1000 Ljubljana, Slovenia.

UDC: 616.621.31: 618.173-085

Postmenopausal symptoms occur due to hormonal changes. Approximately one third of women will be free of any complaints, 35 % have minor symptoms that can be easily endured while in 30 % of women the severity of complaints requires medical attention.

Generally, acute symptoms occur a few months prior to the onset of menopause. These include vasomotor symptoms, sleeping disorders and psychological problems. The most frequent complaints occurring a result of vasomotor instability are hot flushes, night sweating, palpitations and headaches. Pathophysiology of vasomotor symptoms has not been fully explained yet. Most probably they should be ascribed to hypothalamic termoregulatory mechanism disorders. The vasomotor symptoms persist for more than 5 years in 25 % of women, while in a small group they can even last for the rest of life.

Various epidemiological studies have shown that women between 45 – 50 years of age are more prone to depression than males. It has also been proved that depression symptoms are encountered less frequently in females who are maintained on estrogen replacement therapy after ovariectomy.[2] Other authors support the theory that depression associated with menopause occurs because of hot flushes and other difficulties.

The symptoms that occur later includ changes in the urogenital tract. Amog these, dry vagina, dyspareunia and atrophic vaginitis are most disturbing. Local atrophy is one of the causes of urethral syndrome, which manifests itself with dysuria and frequent urination without evidence of urinary tract infection.

Chronic changes become evident a few years after the menopause. They include osteoporosis and cardiovascular disorders. Osteoporosis is characterized by a gradual decrease in bone density and altered microarchitecture of bone tissue. As a result, the bones become fragile and compression fractures of the vertebral bodies, as well as fractures of the neck, femur and wrist are rather common.

Cardiovascular diseases are the leading cause of death in postmenopausal female population. After the menopause, the levels of cholesterol in blood tend to increase. Low HDL and high LDL and VLDL values are associated with an increased risk of cardiovascular disorders which are described as atherogenic lipid profile.[3]

All the described changes can be either diminished or prevented by the use of hormone replacement therapy (HRT). When choosing candidates for hormone replacement therapy all the advantages of such treatment should be weighted against its possible drawbacks. Thus, HRT is considered suitable in women with evident symptoms of estrogen shortage, as well as in those with risk factors for osteoporosis and in those with familial history of caridovascular disorders. HRT is introduced immediately after the cessation of ovarian function or even in premenopausal period – on the occurrence of problems. The medications used should contain minimal doses of estrogen. Conjugated equinous estrogen or estrogen sulphate can prevent the onset of osteoporosis already at a dose of 0.625 mg. Estrogen is combined with progesterone for 10–14 days per month cycle.[4] Women, who still have the uterus, should receive combined estrogen-progesterone preparations, while those without it, can be given estrogen alone.[5] Prior to the introduction of HRT, potential recipients should undergo a thorough gynecological check as well as clinical examination of the breast and mammography.

Advantages of HRT

The replacement of sexual hormones in menopause has several advantgates. It can significantly reduce the vasomotor symptoms and psychogenic problems. The urogenital symptoms gradually disappear. The risk of cardiovascular diseases is decreased by 30–70 % while an already existing coronary disease is associated with a longer survival. The positive effect is increased by years of HRT use.[6] Exogenous estrogen inhibits bone resorption and reduction of bone density, this effect being most beneficial in the first 5 menopausal years when the loss of bone mass is most rapid. It has been proved that 5 years of continuous estrogen use can protect women against osteoporosis related bone fractures.[7] The results of Harvard Nurses Health Study have shown that women with surgery entailed menopause who were receiving HRT had significantly less cardiovascular disorders than those without postoperative HRT.[8]

HRT and carcinomas

While estradiol and estrone induce the epithelial proliferation, progesterone and the end product of estrogen metabolism reduce the proliferative effect

of estradiol and estrone. Progesterone protects the organism against hyperstimulation by decreasing the level of nuclear estrogenic receptors, as well as by inhibiting the conversion of androsterone into estrone and thus reducing the number of mitoses. Moreover, it potentiates the activity of 17-ß estradiol-dehydrogenase whic changes estradiol into the less active estrone.[1]

Breast cancer

In the developed countries, breast cancer in postmenopausal period is the most frequent cancer in females. Its incidence increases by advancing age. Therefore, possible influence of estrogen on the onset of breast cancer deserves our full attention. Nevertheless, despite numerous studies, the association between HRT and breast cancer risk has not been thoroughly clarified yet. There is a great number of epidemiological studies concerned with this pressing issue. However, more than 20 case-control studies and 4 cohort studies report inconsistent results with either increased or decreased relative risk, or no effect at all.[9] Comparison of the results is difficult and unreliable due to the fact that estrogen alone was used as HRT in a majority of large series studies, while in some others HRT consisted of a combination of estrogen and progesterone. Also, the number of cases in individual studies was different, and so was also the duration of treatment. Inconsistency of the results obtained is therefore more than obvious.

Some of the published reports claim that the risk of breast cancer development increases by the duration of HRT use, and that the relative risk (RR) increases to 1.5 after 20 years of therapy. The results of a Swedish cohort study refer to 23000 women followed up for 5–7 years. RR was found to have elevated to 1.1. After more than 9 years of HRT use RR increased to 1.7.[10]

So far, we can conclude that the epidemiological data obtained till now, fail to point out a clear correlation between HRT and the onset of breast cancer.[11]

The question remains, whether HRT is indicated in women with familial history of breast cancer. A presumably higher risk should be associated with the occurrence of breast cancer in the premenopausal period. After the menopause, the risk for all women of the same age group remains the same. It is believed that the risk of breast cancer in women with familial history is not associated with the use of HRT.[7] Therefore, in the postmenopausal period there is no specific group of women in whom the use of HRT would be contraindicated.

Endometrial carcinoma

In the middle of the 70's, there were several studies published which reported an association between the use of estrogen and an increased relative risk of endometrial carcinoma. After 5 years of therapy with estrogen alone, the RR amounted to 4.1, while after 10 years of use it increased to 11.6. Those data appeared rather alarming, and as a result, they started to combine estrogen with progesterone. It was found that the addition of progesterone in the duration of 12–14 days per month can completely inhibited the development of cystic and adenomatous hyperplasia, and RR for endometrial carcinoma decreased to 0.2–0.4.[11, 12] These results were derived from a large number of clinical and epidemiological studies.

Ovarian cancer

Few case-control studies were published on possible correlation between HRT and ovarian carcinoma. In a majority of these the corrrelation could not be confirmed, while some authors report on a minimally increased risk associated with long-term use of HRT. Furhter studies are required to provide an answer to this question.[13]

Gastrointestinal cancer

According to some epidemiological studies, some reproductive factors may play a role in the etiology of colorectal carcinoma. Estrogen and progesterone receptors were found in normal as well as carcinomatous epithelial cells of the colon.

There were 15 studies published on the correlation between HRT and colorectal cancer. Based on the data obtained, it can be concluded that HRT does not represent a risk factor for the development of colorectal cancer in females. Some authors have even manged to prove a protective effect of HRT.[14]

Estrogen receptors can also be found in a certain proportion of gastric cancer. Nevertheless, there is no evidence that sexual hormones would play any

role in gastric carcinogenesis. There is no information available on a possible correlation between HRT and gastric cancer.

Conclusion

The use of HRT in postmenopause decreases the morbidity and mortality of caridovascular diseases. It alleviates the menopausal symptoms and prevents the onset of osteoporosis.

In hysterectomized women estrogen therapy without the addition of progesterone is sufficient, while in theose with the uterus preserved, estrogen should be given in combination with progesterone.

In conclusion, we believe that the favorable effect of estrogen on the morbidity and mortality of cardiovascular diesases outweighs the potential risks. Presently, we lack sufficient data which would enable us to identify the group of patients in whom the use of HRT would entail a potential risk.[15]

HRT should not be regarded as an elixir of eternal youth and the solution of all menopause-related problems. It is not well tolerated by every woman and it is not completely free of any danger. Many women cannot benefit from it owing to the fear of adverse side effects.

While the doctor is the one who should inform the woman on the effects, advantages and potential risks of HRT, the woman herself should decide whether to use the suggested therapy or not.

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