

Hormone Replacement Therapy

This report reviews the scientific evidence on Hormone Replacement Therapy (HRT). It is one in a series of scientific reports published by SBU (The Swedish Council on Technology Assessment in Health Care).

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The Summary and Conclusions are endorsed by the SBU Board of Directors and the SBU Advisory Committee.

Hormone Replacement Therapy

An Evidence Based Review

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Summary and Conclusions of the SBU Report on:

Hormone Replacement Therapy

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May 2002

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Report: Hormone Replacement Therapy • Type: Evidence based review
ISBN: 91-87890-77-1 • Report number: 159 • Publishing year 2002



SBU Summary and Conclusions

Introduction

Estrogen is a female sex hormone that has long been used to treat the symptoms of menopause. Estrogen is also used for preventive purposes to counteract the risks for cardiovascular disease and osteoporosis-related fractures.

The medical effects of estrogen treatment are known to some extent but much remains to be learned, particularly concerning long-term effects and risks. Using scientific methods to acquire precise knowledge about the risks and benefits of estrogen treatment is a complex endeavor, in part because treatment is not uniform. The types of agents, duration of treatment, dosage, and combinations with other hormones vary. Acquiring a comprehensive assessment of the entire field requires very large studies that can demonstrate the effects on total mortality.

Critical review of the scientific literature has identified many gaps in knowledge. A detailed accounting of these gaps appears in the chapters of this report. Clearly, further studies are needed within the broad area of hormone replacement therapy after menopause.

In 1996, SBU published a scientific review of estrogen treatment following menopause. Since then, several important studies have been published in the field. Hence, there was reason to review the recent scientific literature and determine the extent to which the new findings affect the conclusions presented in the earlier SBU review. The new findings have only a minor impact on the previous conclusions. In some cases, the scientific evidence has become stronger (risk for breast cancer from long-term treatment) while in other cases the uncertainty identified in the earlier report remains (effect on cardiovascular disease and stroke).

Concepts related to estrogen treatment

The earlier report used the term *estrogen treatment* as a general expression for treatment with hormones during and following menopause (the final menses). In the international scientific literature, and in general discussion, this term is increasingly being replaced by the American concept of *Hormone Replacement Therapy* (HRT). In Sweden and in most Western nations, HRT covers routine estrogen treatment where estrogen is administered along with gestagen. In cases where estrogen is administered alone, the abbreviation ERT (*Estrogen Replacement Therapy*) is used. These internationally accepted terms are used in this report since they cover the current level of knowledge more broadly than the previous term.

Background

Women undergo hormonal change between the ages of 45 and 55 years. The production of female sex hormones successively declines, as does fertility, which eventually ceases completely. An important event in this course is the final menses (menopause).



Symptoms associated with menopause

Hot flushes and sweating

A high percentage of all women (75%), experience symptoms involving sweating, heat sensation, and hot flushes for several years following menopause. In some cases, these symptoms are hardly noticeable, while in others they can be severe. The symptoms cease spontaneously with time. In some women, symptoms may persist for more than a decade.

Vaginal and urinary tract symptoms

Vaginal and urinary tract symptoms may appear following menopause. Vaginal symptoms include dry or burning sensations, itching, pain during coitus, and transient bleeding or discharge. Urinary tract symptoms may include a burning sensation during micturition, frequent urgency, repeated urinary tract infections, and urinary incontinence. These symptoms are reported to appear in up to one half of all women during menopause. The symptoms become more common a few years following menopause. Untreated, these disorders can become permanent.

Increased risk for health disorders following menopause

Cardiovascular disease

Myocardial infarction and stroke dominate as causes of morbidity and mortality among Swedish men and women from upper middle age and onward. On average, women experience these problems approximately 10 years later than men do. Female morbidity from these diseases is relatively low prior to menopause. Thereafter, it increases rapidly. This could suggest that estrogen production may offer protection against vascular diseases. However, no direct correlation has been found between the amount of estrogen in the blood and the risk for cardiovascular disease.

The interaction among the effects of estrogen on blood vessels and blood and cardiovascular disease is highly complex. Despite extensive investigation, knowledge in this field remains limited, which motivates further scientific studies.

Osteoporosis and increased risk for fracture

The skeleton also changes following menopause. Throughout life, the skeleton is involved in a dynamic process where the degradation of bone is followed by new bone formation in a well-regulated interplay among the various cells of the skeleton. These cells are influenced directly and indirectly by estrogen. Estrogen deficiency leads to a loss of bone mass, impairs the development of bone structure, and reduces bone strength. This increases the risk for bone fracture, even under moderate stress. The risk increases with increasing age. Fractures of the vertebra and femoral neck are more common in elderly women than in men, which correlates to the successive decline in estrogen production in elderly women.

Estrogen agents

Estrogen agents are available in several forms and strengths. Administering low doses – or less active agents – can be sufficient to achieve effects on vaginal and urinary tract symptoms. However, low doses do not have an effect on the heart, vascular system, or skeleton, nor on hot flushes and sweating. Such effects require higher doses or more active agents.

Estriol is an estrogen agent of low potency and is often given for vaginal or urinary tract symptoms. Estradiol is a naturally occurring estrogen agent of moderate potency. It is most commonly used to treat climacteric problems. To date, treatment has usually been given as tablets, but treatment can also be delivered through patches, estrogen gel, or local vaginal treatment. The latter forms act more directly and impact less on the liver, reducing the risk for side effects.

To counteract the risk for cancer in the endometrium, long-term administration of estrogen must be combined with gestagen. The combination of estrogen and gestagen can result in vaginal bleeding and side effects such as a sensation of tension in the breast or mood changes. This may contribute toward not taking the agent as prescribed, ie, lower compliance.

HRT for Climacteric Symptoms

Introduction

The most common treatment for climacteric symptoms is estrogen replacement therapy. Long-term estrogen treatment can overstimulate the endometrium and increase the risk for bleeding and, with time, cancer. To counteract these risks, treatment is usually combined with gestagens (HRT).

Hormone replacement therapy for climacteric symptoms and vaginal and urinary tract disorders is given only to women with symptoms and not for preventive purposes. In general, treatment does not last more than 5 to 10 years. Low-dose treatment is often given for a longer period to treat problems involving the mucous membranes.

Hot flushes and sweating

Controlled studies have shown that different forms of estrogen have good effects on symptoms and quickly relieve problems, for up to 10 years of treatment. Further controlled studies of HRT/ERT have been published since the previous SBU report and show good effects on symptoms.



The effect remains as long as treatment continues. It is independent of whether estrogen is given alone (ERT) or in combination with gestagen (HRT). It is also independent of the mode of delivery. Studies also show that HRT does not influence body weight.

Recently, substances have been developed with effects similar to those of estrogen, but they have been studied to a relatively minor extent. The same applies to other hormone combinations, such as estrogen–androgen.

Vaginal and urinary tract symptoms

Treatment with low dose estrogen has good effects on vaginal or urinary tract symptoms. Treatment can be delivered locally. Also, treatment appears to reduce the risk for repeated urinary tract infections. Treatment is also motivated for other urinary tract symptoms such as frequent urgency, urge incontinence, and mixed incontinence. Scientific evidence on the treatment of urinary tract symptoms is more limited than evidence concerning the effects on vaginal symptoms.

Studies published since the previous report have somewhat reduced the uncertainty concerning the effects of HRT on vaginal and urinary tract symptoms.

Life quality and mood

Quality of life may decline during menopause, mainly due to the accompanying symptoms. Several new studies on HRT have shown that HRT has positive effects on the quality of life. The extent to which these positive effects override the effects of the special symptoms of menopause is unclear.

HRT as Preventive Therapy

A large part of the new scientific literature addresses the role of HRT in preventing cardiovascular disease, osteoporosis, and fracture. Many major studies have been published, but the results of these studies do not definitively answer the questions.

Preventing heart disease

Several studies have attempted to estimate the effects of HRT in preventing heart attacks. Most of the studies concern women who reported regular use of estrogen agents after menopause. These groups were compared to other groups of women who were not treated with estrogen. The groups who received HRT generally had a lower rate of heart attacks or less mortality from heart disease than the control groups. The patient composition in these studies makes it difficult to draw conclusions from the results. These problems have been investigated further since the previous report, and new studies have controlled for several factors that may play a role. This has rendered the assumption, ie, that HRT has preventive effects, less plausible.

A controlled study of HRT in women *with previous heart disease* has shown that treatment did not reduce the risk for recurrence. Controlled studies of HRT in women *without previous symptoms involving the cardiovascular system* are underway, but have yet to be published.

It can be noted that the two large American organizations for heart specialists, ie, the American Heart Association and the American College of Cardiology, reviewed the literature in a report to practicing physicians in the United States during the summer of 2001. They found insufficient evidence to recommend using HRT to prevent the risks for cardiovascular disease in aging women.

Opposed to previous findings, a general assessment of all studies would now suggest that estrogen treatment probably does not protect against myocardial infarction. Further studies are needed to confirm this conclusion. Such studies are underway in the United States and England.

The earlier conclusion – that women who have experienced early menopause, eg, due to surgical removal of the ovaries, should be treated with estrogen – has not changed.

As in the earlier report, studies aimed at assessing the preventive effects on stroke have not shown any such effects.

The current state of knowledge suggests that HRT should not be used for the specific purpose of preventing cardiovascular diseases.

Preventing fracture

Many factors contribute toward reducing the amount of bone tissue in the skeleton during aging, leading to osteoporosis and a greater risk for fracture. Lowered production of estrogen following menopause leads to a period of more pronounced bone loss. Hence, it is important to study the effects of HRT on bone mass and the incidence of fracture following menopause. The previous SBU report showed that most epidemiological studies found fewer fractures during ongoing estrogen treatment – the risk fell by nearly half when treatment was started in patients in their 50s, but the effect tended to decline with increased time after the final treatment.

Several studies have been published since, but without resolving the problem. The controlled studies that have been published have presented results that are difficult to interpret and show different effects from HRT in younger and older women. It appears that HRT in younger women helps prevent bone fracture and the loss of bone mass. However, studies that were conducted on older women have not shown the same favorable effects. The question of what impact the duration of treatment has on bone mass or risk for fracture remains.

No studies have yet been published on the effects of HRT in the oldest age groups. The median age for hip fracture in women is somewhat over 80 years. Although bone tissue should react in a similar way at these ages as in younger women, it is plausible that other effects and side effects can differ. For example, how an individual complies with a given prescription plays a role.

The evidence is still unclear regarding the extent to which HRT actually prevents osteoporosis or bone fracture, except in certain risk groups.

A project by SBU is currently studying the scientific literature on osteoporosis. A report on this topic will be published in 2003.

Preventing dementia

Some studies have reported observations that HRT influences general mood and well-being. Hence, it is possible that HRT might prevent, or at least delay, the development of age-related dementia. Some limited studies have shown that HRT may influence cognitive functions, but it is too early to draw any conclusions from these studies.

Risks Associated With HRT

Risk for blood clots in veins

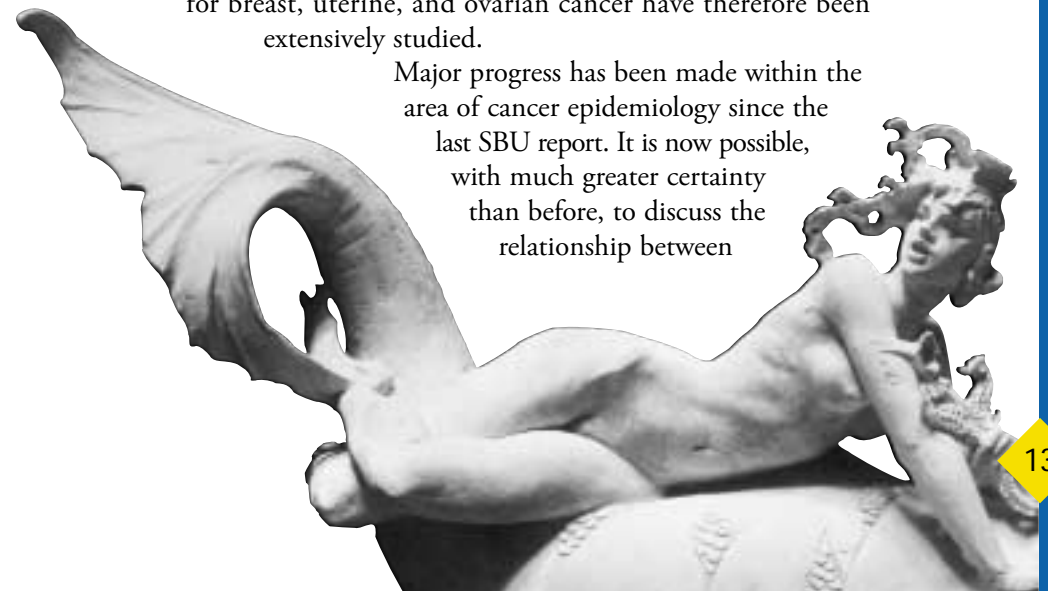
Estrogen influences both the coagulation capacity of the body and its potential for dissolving blood clots in the veins. Hence, HRT increases the risk for venous blood clots and possible embolization in the pulmonary arteries.

Recent studies have shown that HRT increases the risk for developing blood clots in veins by two- or three-fold, mainly during the first years of treatment.

Risk for cancer

Sex hormones affect the breast, endometrium, and ovaries. Growth, maturity, and function are mainly regulated by hormones, primarily estrogen and progesterone. Potential effects from HRT on the risks for breast, uterine, and ovarian cancer have therefore been extensively studied.

Major progress has been made within the area of cancer epidemiology since the last SBU report. It is now possible, with much greater certainty than before, to discuss the relationship between



HRT and the incidence of various types of cancer.

Since cancer cannot be viewed as a single disease, and knowledge about the background and incidence of cancer in different organs varies, it is not possible to render a universal judgement on a particular factor's (in this case HRT) impact on cancer incidence generally. Relatively well-founded knowledge is available concerning the increased risk that HRT can represent for breast cancer, uterine cancer, and ovarian cancer.

Some data have also emerged to suggest that some types of cancer appear less frequently in women with HRT than in controlled series.

Breast cancer

Epidemiological studies addressing the association between HRT and breast cancer clearly show an increased risk for development of breast cancer. This risk appears only after several years of treatment. All of the agents studied increased the risk for breast cancer after 6 to 10 years of treatment. The risk level increases with the duration of treatment time, from 1.5 to 2.5 at 10 to 15 years of treatment. The association between estrogen treatment and breast cancer appears to be highest at or near the time of ongoing treatment. Adding gestagen does not appear to reduce the risk. Some studies show that the types of cancer which appear after estrogen treatment have a less aggressive natural course than tumors which appear in patients not treated with hormones.

Endometrial cancer

All of the estrogen agents studied, when administered without gestagen, increase the risk for cancer in the endometrium. This risk is dose dependent and depends on the

duration of treatment:

- It increases measurably after 2 to 4 years of treatment.
- It increases successively with the duration of treatment and reaches a tenfold increase after more than 10 years of treatment.
- It declines after the conclusion of treatment, but some risk remains.

The addition of gestagen reduces risk, and with more continuous treatment it completely prevents increased risk.

Ovarian cancer

The previous report offered no data on this type of cancer. New studies have been conducted because, in theory, hormone treatment could influence the risk for ovarian cancer.

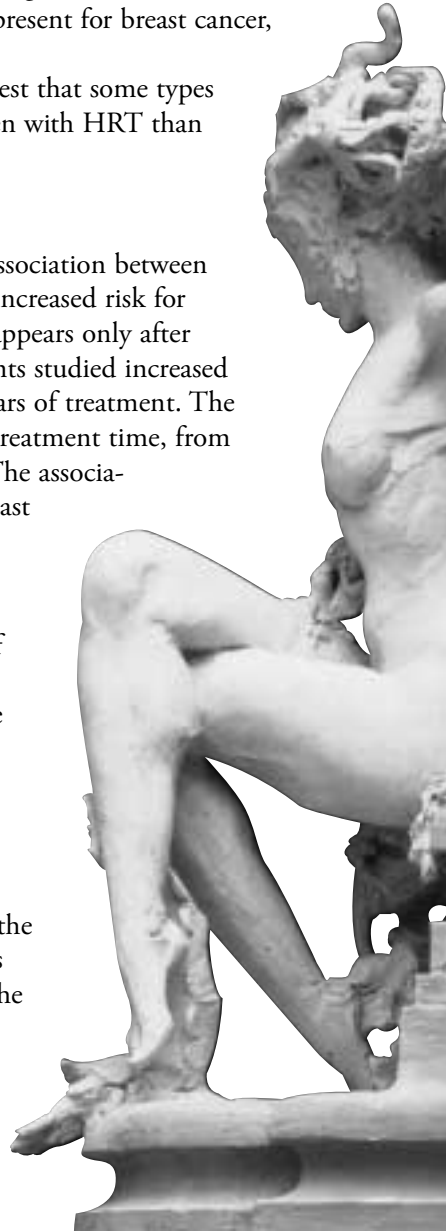
Some evidence suggests that HRT can increase the risk for this type of cancer after several years of treatment. More studies are needed to confirm this risk.

Colon cancer

The previous report provided no data on this type of cancer. New studies have been conducted on this type of cancer. There is no evidence of increased risk for colon and rectal cancer following HRT. Rather, some data suggest there are protective effects. However, these data are unconfirmed.

Skin cancer – malignant melanoma

The previous report provided no data on this type of cancer. New studies have been performed on this type of cancer, but the evidence is not conclusive.



Health Economics

The scientific literature provides no evidence for any definitive conclusions concerning the cost–utility of estrogen treatment following menopause. The main reason is that economic studies have included different groups of patients and risk factors, rendering it impossible to assess clinical effects with any certainty.

The cost of estrogen treatment is moderate. Even with relatively minor effects, treatment of symptoms should be cost–effective. This may apply to HRT for climacteric symptoms. More recent and more complex treatment approaches, and new variants of drugs with estrogen effects, should be studied to assess cost–utility, particularly since these agents will probably be more expensive to use.



Conclusions

- ❑ HRT has many advantages, but also some risks. Women themselves – after being thoroughly informed – should decide on the possibility of treatment.
- ❑ Treatment using estrogen agents of moderate potency have good effects on the climacteric symptoms of hot flushes and sweating.
- ❑ Treating climacteric symptoms during a limited number of years has a confirmed benefit, and none of the scientific evidence shows that it leads to any measurable increase in risk for breast cancer and endometrial cancer, assuming that treatment is designed in accordance with accepted recommendations.
- ❑ Treatment using estrogen agents with low potency has good effects on vaginal and urinary tract symptoms.
- ❑ There is insufficient scientific evidence to make general recommendations on hormone therapy aimed at prevention in symptom-free women following menopause, although HRT can preserve bone mass around the time of menopause.
- ❑ Long-term ERT increases the risk for endometrial cancer, but this increase can be counteracted by the addition of gestagens.
- ❑ Longer treatment periods are associated with a risk for breast cancer. The risk depends on the duration of treatment, but it is moderate even in long-term treatment. The potential benefits of HRT must be balanced against the risks, hence it is important to thoroughly inform women who are deciding about treatment.

It may be difficult to explain why the risk for breast cancer increases from HRT. The magnitude of this risk during and following treatment should be studied in terms of the difference in absolute risk between no treatment and treatment. It is estimated that the risk for developing breast cancer from age 50 to 75 years in women not treated with hormones is 7 cases per 100. This risk can increase to 9 cases per 100 with hormone replacement therapy.



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- SBU's assessments shall cover the medical aspects and the ethical, social, and economic consequences of disseminating and applying medical and dental technologies.
- SBU's assessments shall be compiled, presented, and disseminated in such a way that all affected parties have access to the information.
- SBU shall contribute, through informational and educational initiatives, toward ensuring that the knowledge gained is used to rationally utilize available resources in health care.
- SBU shall draw on national and international experience and research findings in the field and shall serve as a focal point for health technology assessment in Sweden. This effort shall be managed in a way that secures success and respect for the organization, both domestically and internationally.