

# Hormonal replacement therapy and gynecological cancer

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## Summary

The problem of quality of life and lifestyle in elderly women is today a very important social problem all over the world but particularly in rich western countries.

Life expectancy of the population will be longer and longer in the future and for both females and males the biological involution correlated with the aging process must be delayed.

The gonadal hormones stimulate the healthy state of the entire body (heart, skin, brain, bones, urogenital apparatus and so on) and consequently hormonal replacement therapy (HRT) is mandatory.

In women the biological clock of menopause allows us to intervene at the right time, with personalized estrogenic, estroprogestinic or estroandrogenic treatments.

Health benefits and groundless risks allow today a careful hormonal management even in women treated for gynaecological cancers (breast and endometrium as well).

**Key words:** Menopause; Hormonal Replacement Therapy; Female genital cancers.

As is well known, the lack of ovarian steroids in menopause badly influences the biological and psychological quality of life of women whose average life span is today much longer than in the past. It is now a very serious social problem.

In the past menopause started shortly before the end of a woman's life while today, without adequate management, an ungratifying postmenopause and senility could last a third of her life.

In America, in 1895, life expectancy was about 50 years while today it is close to 80 years [1] and will be longer and longer in the future.

The problem of the increased life-span is not only a personal problem, regarding women (and also men), but a social, very dangerous and expensive problem for everybody and for welfare states too.

Nowadays a good quality of life *must* be maintained until a very advanced age by a healthy lifestyle - proper nutrition (low fat and calories), no (or low) alcohol and cigarettes, regular physical activity and sports, social and work interests and, last but not least, personalised *Hormonal Replacement Therapy* (HRT).

This is not only true for women but also for men, in whom andropause is less noticeable but nevertheless equally dangerous.

In rich countries, as well as in western Europe, longer life expectancy for women (and for men...) could be of little gain without the correction of gonadal steroid deficiency (ovarian, testicular) because of many health problems: physical and psychological depression, disabilities, bone loss, cardiovascular disease, poor memory performance and cognitive processes, Alzheimer's disease and so on.

In menopause different management strategies of HRT are followed: combined or sequential estro-progesterone

therapy (EPRT), combined estrogen-androgen treatment (EART) or only estrogen treatment (ERT); also for long-term use (LTERT-LTHRT).

The biological effects of estrogen have been well known for many years.

Estrogen deficiency is characterized by neuroendocrine and psychological alterations, endocrine metabolic disorders, genital urinary involution (atrophy, dystrophy, dyspareunia, nocturia, vaginitis, cysto-urethritis), urinary urge and stress incontinence, pelvic floor weakness, utero-vaginal prolapse, reduced breast size and consistency, bone loss (up to osteoporosis and related fractures), cardiovascular diseases, brain, memory and cognitive function reduction.

The treatment with combined estrogen-androgen association - particularly important in late postmenopause or in women with surgical menopause, lacking ovarian androgen production - stimulates more interest in life, also in sentimental, emotional and sexual life.

Unfortunately, still today, there is a lot of fear among women and physicians too, about hormonal side-effects and also about their oncogenic activity, particularly for breast and endometrial cancers.

Perhaps estrogen can stimulate the growth of preexisting tumors but does not generate tumors as shown by many researchers [26].

However, large clinical experiences throughout the world over the past 50 years have demonstrated that the cost-benefit balance of HRT is undoubtedly favourable if compared with the hypothetical risks, particularly carcinogenic, still today undemonstrated even in the largest epidemiological studies [2-13].

Greater incidence of breast cancer in users of combined or sequential estrogen-progesterone replacement [14-18], of estrogen only replacement [18-21] or of long-term estrogen replacement [1] has not been reported but nevertheless some authors are wary [10, 22, 23].

Other authors believe that more complete and large epidemiological studies will be needed, for at least ten years, to have valid conclusions [24, 25] but the large case series already published are sufficient, in our opinion, without any doubts [26].

In postmenopause the advantageous effects of estrogen have been largely demonstrated: estrogen reduces the incidence of heart disease, which in women in menopause reaches the same level as in men [27, 28, 29]. Estrogen reduces arterial hypertension and atherosclerosis, hyperlipidemia and hypercholesterolemia and LDL cholesterol levels [30, 31] which are very dangerous for coronary atherosclerosis [32].

Estrogen also averts uro-genital dystrophy, urinary incontinence [33], utero-vaginal descensus, osteoporosis [34, 35, 36] and Alzheimer's disease [37, 38].

In our opinion LTHRT is mandatory, obviously with correct follow-up of the users while short term hormonal replacement therapy (STHRT) is inadequate to ensure a good health status in the long postmenopausal life.

After decades of clinical experience worldwide – and also in our experience – the use of estrogen alone or combined with androgen, in long-term personalised treatments, beginning during postmenopause and continuing throughout old age, is increasing daily.

On the contrary, association – combined or sequential – of estrogen and progesterone is under discussion because of the frequent side-effects [11, 21-45].

Many Authors, as well as ourselves [11], prefer to use progesterone only for a short period of time, in younger women – under 55-60 years in order to have menstrual bleeding, more for psychological well-being than for endometrial protection.

In fact, progesterone reduces the positive effects of estrogen against coronary heart disease [45, 46], increases LDL cholesterol levels [47-50], modifies the clearance of insulin [39, 42], insulin resistance and glucose tolerance [13, 20], while it has not been demonstrated that it protects against breast cancer [21, 30].

In the literature we have enough information about STHRT but not about LTHRT – in personalised modulated types, doses, formulations and administration routes.

Undoubtedly, in women with an intact uterus progesterone plays an important role in avoiding endometrial hyperstimulation-sometime dangerous (simple hyperplasia, cystic or adenomatous hyperplasia up to well-differentiated adenocarcinoma) but the side-effects, like bleeding and poor compliance, are often responsible for the discontinuation of HRT [40].

Consequently, we prefer to use only estrogens but with careful endometrial checks by ultrasound – every six months – and, if needed, target biopsy samples (aspiration curettage) once every 1-2 years.

Today the possibility of non-invasive checks of the endometrium allows us to harmlessly avoid progesterone association, particularly in the elderly.

Otherwise, in particular cases of endometrial hyperstimulation we use progestagen for only two-three months every year to allow endometrial shedding by menstrual bleeding.

With ERT or LTERT the incidence of simple endometrial hyperplasia in some studies has reached 50% of cases [28] but neoplastic degeneration is rare [26], usually well-differentiated, and with a good prognosis [51].

In our case series over 25 years we have observed, sometimes, simple endometrial hyperplasia or glandulocystic and even adenomatoid hyperplasia but no neoplasias [26].

In our opinion and experience, close and careful checks, neither expensive nor invasive, allow safe LTERT and are very useful in monitoring the general health condition and genital-well-being, particularly for prevention and early detection of gynecological cancers.

In fact HRT obliges women to be responsible for their own health and for their quality of old age.

HRT and ERT now are also employed in women who had genital cancer, even breast cancer [9, 40, 53-57]. We have followed this strategy for many years and have never observed relapses nor metachrone tumors.

There has been a lot of research on HRT and ERT in women treated for breast cancer [9, 57, 60] with no reports of complications.

In every case histotype, grading, hormonal receptors and all aggressiveness tumor factors must be carefully evaluated and adequate checks performed.

Even in women treated for endometrial cancer, HRT or ERT are normally applied by many gynecologists [51, 52, 57] and by ourselves; the lack of a uterus allows harmless LTERT.

Nevertheless tumoral aggressiveness factors must always be considered and patients carefully followed.

Cervical, ovarian and vulvar cancers are not hormone-dependent and consequently there is no fear of LTERT [59, 61, 62].

We strongly recommend estrogen replacement therapy in ovarian cancer patients because estrogens block the hypophysis, reducing the levels of gonadotropin which can stimulate and increase the aggressivity and the high mitotic activity of some ovarian cancer cells.

In our clinical experience as in others [64], EART appears very useful in personalized treatments.

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In conclusion, we believe that today a personalised modulated LTHRT is the elective management to preserve quality of life for the elderly, avoiding biological breakdown and disease correlated with old age.

The preliminary results of biological estrogen response tests to modulate doses and routes of administration are interesting [64].

It is mandatory to provide *precise information to women* that the advantages are undeniable while the risks, even carcinogenic, are in small percentages and *without statistical significance* [26].

The patients must have the clear perception that HRT is not “*a sinister marketing programme designed to medicalize the menopause*” as provocatively hypothesized by Utian [40], but, in the cost-benefit balance, it is the only way for women to have psychophysical and biological

well-being, even in the most elderly and in cancer survivors.

Bleeding, fear of breast cancer and progesterone side-effects are the most frequent factors – in women not well-informed or without good rapport with their gynaecologist – for discontinuing HRT.

On the basis of worldwide experience, as well as ours, we believe the time is right to employ only estrogens in personalized administration (ERT and LTERT) even in genital and breast cancer survivors. In our opinion progesterone can be used only in selected cases, not routinely.

The psychological, cultural and social personality of each patient as well as individual risk factors such as hypertension, obesity, smoking – or familiar, genital neoplasia incidence – must be carefully evaluated to select a personalized hormonal management.

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