Hormone replacement therapy and autoimmune diseases

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Autoimmune diseases affect more frequently women. Hormonal variations in menopause modify the incidence and trend of autoimmune diseases. The dramatic decrease in estrogen levels due to ovarian exhaustion and the constant DHEA production are regarded as protective hormonal factors even though menopause has multifactorial traits: age, age at menopause onset, duration and gravity of the disease, estrogen receptor alteration, genetic alteration, interaction between estrogen and androgen receptors, progesterone and prolactin.

Hormone replacement therapy (HRT) does not seem to be linked to relapses nor to a new disease in patients with rheumatoid arthritis. It is quite controversial though the use of estrogens in the presence of systemic lupus erythematosus. In this case, the risk of low to medium disease relapse in women undergoing HRT is quite significant. The use of NOR progesterone derivatives and of transdermal estrogen can be more effective than E.E.C.-M.A.P. system. SERMs have proven to be an effective option for the treatment of osteoporosis which is often linked to autoimmune diseases. Tibolone appears to show tissue specific androgen activity with no added mammary risk.

HRT needs to be administered in low dosage to patients with autoimmune diseases and for no longer than 2 years (WHI).

An alternative to HRT are: microdose TTS estrogen therapy for osteoprotection, topical estrogen for genital dystrophy, progestins for vasomotor syndrome.

KEY WORDS: Autoimmune diseases - Hormone replacement therapy - Menopause - Androgens - Estrogens.

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Epidemiology of autoimmune diseases

About 8% of the world population is affected by autoimmune diseases, of which 78% are women. The female to male autoimmune disease ratio ranges from 2:1 (rheumatoid arthritis) and 9:1 (systemic lupus erythematosus). The most common examples of autoimmune diseases are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and sclerodermia. These diseases affect more frequently over age 40, a period during which the main hormonal changes occur.

RA is roughly 3 time more frequent in women than in men, reaching the highest incidence in the fifth decade of life. The gap between men and women decreases with age to the extent that, after age 75, RA incidence is higher in the male population.

The average sclerodermia ratio between females and males is 3:1 with slight changes for the various age groups.

Among autoimmune diseases, SLE has the earliest onset with a female to male ratio of 9:1 between the end of the first decade and the beginning of the fourth decade of life (1).

Estrogens and autoimmune diseases

Sexual hormones do play a role in the immune answer, even though further studies are needed to fully assess this role. On the basis of the inflammatory effect, two groups of sexual hormones can be identified: estrogens and prolactin with pro-inflammatory effect; androgens and progesterone with anti-inflammatory effect.

Estrogen-androgen interaction can be modified by different physiological, pathological and therapeutic conditions such as the menstrual cycle phase, pregnancy and postpartum period, mature age, menopause, circadian rhythm, chronic stress, inflammatory status or cortisone/hormone therapy.

As a matter of fact, autoimmune diseases are characterized by a change in the estrogen to androgen ratio, with a prevalence of the estrogen pool.

High levels of estrogen have been observed in the synovial fluid of patients affected by both SLE and RA. The cause is the action of aromatase on peripheral tissues. Inflammatory cytokines, like TNFα, IL-1 and IL-6, which are produced by macrophages, stimulate the action of aromatase which is responsible for the conversion of androgens (DHEA, testosterone, progesterone) into 17-β-estradiol. The latter acts on immunocompetent cells activating the macrophages in the production of pro-inflammatory cytokines. A vicious and self-stimulating cycle is thus started.

The action of sexual hormones on the immune system is much more complex.

Sexual hormones can exert a direct or indirect action on the immune system. The indirect action is linked with a genetic polyclonal activation mechanism exerted by estrogens (E2) which leads to an increase in the antibody production and to a change in the relation of Th1 and Th2 cytokines.

The direct action mechanism, instead, depends on a different set of factors such as the type of receptor on which hormones act, the hormone concentration, the type of target cell and the variety of metabolites produced.

Immunocompetent cells (lymphocytes T and B, monocytes, macrophages and dendritic cells) are associated with two types of estrogen receptors, ERα and ERβ receptors. ERα receptors comprise a higher immunostimulant effect.

Also plasmatic hormone concentrations determine opposite effects: high E2 levels have anti-inflammatory effects whereas low E2 levels have pro-inflammatory effects.

The type of final metabolite produced is also important. The 17-β-estradiol, which is produced by the peripheral conversion of androgen into estrogen by aromatase, can be converted into 16-a-OH-estrone, which has pro-inflammatory effect, or into 2-OH-estrogen, having opposite effect (1-5).

Effects of autoimmune diseases on menopause

Autoimmune diseases can have a direct or indirect effect on the cardiovascular, neurological, skeletal and genito-urinary systems. They can cause cognitive deficits, vasomotor symptoms, osteoporosis and genito-urinary dystrophy. Autoimmune diseases are responsible for a higher incidence of premature menopause.

Premature menopause is a condition of amenorrhea caused by hypergonadotropic ovarian insufficiency before age 40. It affects 1% of the female population, of which 30-50% are women suffering from autoimmune pathology. Other causes of premature menopause can also be traced in enzyme defects, particularly in genetic mutations of receptors for FSH and LH, in genetic anomalies like the fragile X syndrome, or be caused by radiant therapy and chemotherapy.

The presence of anti-ovarian antibodies was demonstrated by two small-sized studies on women affected...
by SLE (16 out of 19 cases) and Sjögren’s syndrome (27%).

Despite the occurrence of antibodies, a higher POF risk has not been demonstrated yet in women with autoimmune disorders.

On the other hand, premature ovarian failure can be associated with the use of alkylating agents such as cyclophosphamide. In women affected by SLE and taking cyclophosphamide, the occurrence of premature menopause is between 11 and 59%. The main independent risk factors are age and cumulative dose (6).

Menopause effects on autoimmune diseases

Menopause can act on organ systems already affected by an autoimmune disease (i.e. cardiovascular or skeletal systems) worsening mortality and morbidity.

Several studies have demonstrated how disease activity and worsening associated with SLE decrease with menopause (6, 7) and how the onset of the disease at a later age has less serious effects (2, 8-10).

There is no scientific consensus whether these changes are actually due to hormonal variations triggered by menopause or to other factors.

The reduced disease activity during menopause can also be determined by the passing of time rather than by hormonal variations (11).

As for rheumatoid arthritis, instead, it has been demonstrated that high levels of estrogen and progesterone are protective for disease activity. Therefore, pregnancy and late menopause are considered protective against the risk of disease development whereas premature menopause and post-partum are often associated with disease worsening. There is an inverse correlation between menopausal age and disease risk. By disease risk it is meant both the risk of developing a new disease and the worsening or higher damage in patients who have already developed the disease (12, 13).

Replacement hormone therapy and autoimmune diseases

Women affected by autoimmune diseases are more likely to develop premature menopause, especially when under cyclophosphamide. Moreover, they have a higher risk of developing osteoporosis, especially patients undergoing cortisone treatment. Lastly, positive antiphospholipid antibodies are associated with arterial and venous thrombosis.

For these reasons, hormone replacement therapy has always been controversial when prescribed to women suffering from autoimmune diseases.

The results of the WHI study on estrogen-plus-progesterin and estrogen-alone effects emphasize the vascular and breast cancer risks. Hence patients with severe vasomotor symptomatology (>50 episodes per week) are prescribed the lowest HRT dose and for the shortest time possible. The same applies to patients suffering from autoimmune diseases (14).

It has already been underlined that estrogen levels and autoimmune diseases are interlinked. In HRT estrogen levels are lower than those of patients with regular periods and amount to 1/6 of the quantity contained in oral contraceptives. The levels of 17-estradiol reached in HRT equal to 1/5 of menstrual peak (15).

As for SLE risk and the use of exogen hormones, consensus in the scientific community has not been reached yet. According to some scientists, factors like menarche or premature menopause, the use of contraceptive hormones or HRT increase the risk of developing SLE (16, 17). According to others instead, there is no association between the use of exogen estrogens and SLE (18-20).

To date, the best scientific evidence is reported in the SELENA study (Safety of Estrogens in Lupus Erythematosus, National Assessment) (21). This study consists of a randomized double blind controlled trial in which 351 women in menopause with stable or inactive SLE have been assigned to placebo group or have been prescribed HRT (0.625 mg per day of conjugated estrogen associated to 5 mg of medroxyprogesterone for 12 days per month) and followed for 1 year. The results of the study show that in women undergoing HRT, light to moderate diseases have worsened again quite significantly in statistical terms, but not severe ones. However, other minor studies, both prospective and retrospective, have reported no increase in the worsening of diseases.

The cardiovascular and thrombosis risk needs to be taken into consideration. It is higher in women with SLE, especially in those with positive antiphospholipid antibodies, and even higher if associated with the use of HRT.

The LUMINA study (Lupus in Minorities: Nature versus Nurture) (22) examined the incidence of thrombotic vascular events in post-menopause women with SLE in relation with the use or not of HRT. The findings of the study, adjusted for the presence of confounding variables between the two groups, show no statistically significant difference. On the other hand, other studies have reported a higher number of thrombotic events in women with SLE undergoing HRT.

In conclusion, before prescribing HRT to patients
with SLE, it is advisable to carry out an accurate analysis of the risks and benefits: disease activity, gravity of menopause symptomatology, likeliness of cardiovascular and thrombotic risks associated with the presence of risk factors such as positive antiphospholipid antibodies.

HRT is currently recommended for women with inactive SLE and negative antiphospholipid antibodies, especially in those with premature menopause and important vasomotor syndrome, possibly as low dose of trans-dermal estrogen and natural progesterone (progesterone micronization or pregan derivates) for the shortest time possible.

In patients with moderate disease activity, the use of non-estrogenic agents like antidepressive or progestins is to be preferred. Failing to be effective, the use of HRT is possible. In patients with active and severe disease or with positive antiphospholipid antibodies, HRT is to be avoided (2, 6).

HRT seems to have a positive effect on osteoporosis, on disease activity and the development of radiologic injuries when associated with rheumatoid arthritis. For this reason, HRT can be prescribed for a short period of time in case of severe menopause symptomatology. The use of HRT for prolonged periods is not justified to control the disease, neither for preventing osteoporosis, nor coronary and thrombotic risk which increases with ageing.

Sjögren’s syndrome is an autoimmune disease which affects exocrine glands causing ocular dryness (keratoconjunctivitis sicca) and dry mouth (xerostomia). Women in menopause can experience ocular dryness in relation with low estrogen levels. Therefore, vaginal and ocular dryness in women in menopause can be misleading for the differential analysis between the autoimmune disease and the menopause syndrome. HRT in women with Sjögren’s syndrome can be treated using low dose DHEA or collyrium with sesame oil 10 g and estradiol-17-β micronized 0.025% (23).

There is not enough evidence on the safety of HRT in women with other autoimmune diseases. Since these diseases are not associated with estrogens, the use of HRT should not raise any concerns. However, antiphospholipid antibodies are frequently positive making HRT inadvisable. The use of HRT associated with rheumatic diseases as dermatomyositis, Sjögren’s syndrome, scleroderma, inflammatory bowel disease seems to be safe in case of stable disease and after carrying out an accurate thrombophilia screening.

In conclusion, women with severe menopausal symptomatology (e.g. vasomotor symptoms, genito-urinary dystrophy, sleeping and sexual disorders) can be prescribed HRT after an accurate screening to detect cardiovascular risk, osteoporosis, cancer and thrombosis. The treatment should be given for the shortest time possible (not more than 2 years), as continuous combined therapy, at low dose, transdermal estradiol-17-β-based and natural progesterone or androgenic progestins (14, 24).

**Alternatives to HRT**

When HRT is inadvisable, there are several therapeutic alternatives to treat some specific symptoms of the menopausal syndrome.

Androgen therapy increases sexual desire and it is even more effective in women with autoimmune diseases for whom the estroprogestin relationship increases and androgen levels decrease.

There are several therapeutic options to be associated with concurrent estrogen therapy: weak androgen through monthly DHEA intramuscular injections, TTs testosterone and oral testosterone. Controlled randomized clinical trials have demonstrated an increase in the sexual desire of women with surgical menopause by using 300 mcg transdermal testosterone on a daily basis (25).

Osteoporosis is a widespread disease on which constant studies are needed to search for new therapies.

Osteoporosis should be treated firstly by acting on lifestyle, diet and calcium and vitamin supplements. Pharmacological treatment should be taken into consideration only at a second stage and always in association with calcium and vitamin supplements. HRT improves bone mineralization and reduces the risk of fractures.

Alternative and sequential treatments to HRT are SERMs (Selective Estrogen Receptor Modulator) and bisphosphonate.

SERMs are a class of drugs that can combine selectively with estrogen receptors. This combination induces sterio alterations which activate specific transcription factors ultimately producing estrogen or antiestrogen effects depending on the kind of tissue. They have bone, mammary and cardiovascular protective effects. They also have a neutral effect on the endometrium but are responsible for the insurgence of vasomotor symptoms, muscle cramps and genito-urinary dystrophy. Since SERMs can produce some side effects like hot flushes, it is more advisable to use them at advanced postmenopausal stage.

Special care should be taken when treating the vasomotor syndrome in patients who cannot be prescribed with HRT.

Alternative therapeutic options consist of antidepressants belonging to the serotonin reuptake inhibitor category of which the most used are paroxetine, clonidine (an alpha-adrenergic antihypertensive agent), progesterone and soy isoflavones (26).
All these pharmacological categories are effective against weak to moderate vasomotor symptoms but do not leap over placebo against severe vasomotor symptoms. Tibolone, a 19 nor-progestin derivative, through three different metabolites, has a tissue-specific agonist/antagonist activity similar to that of SERMs. It exerts a stimulating effect on the bones, brain, cardiovascular and genito-urinary systems whereas it has an inhibitory effect at endometrium and mammary level. It reduces the intensity and frequency of hot flushes according to the dose administered and starting from the 4th week of therapy (2.5 mg per day), reaching the highest peak at week 12. It also improves memory capacity and positively controls the decreasing sexual desire syndrome (27).

A 12-month controlled randomized study included 30 women with stable or inactive SLE after administration of tibolone 2.5 mg per day or placebo. The analysis of the symptoms accompanying hypoestrogenism according to Kupperman index demonstrated a considerable decrease of the symptoms in women prescribed tibolone without a significant increase of the disease level or a risk of relapse. The latter, if present, was moderate or weak (28).

As for time constraints, peri- and postmenopausal disorders are to be treated in the same way as regular patients even though special care should be given to patients affected by stable or inactive autoimmune diseases.

Treatment during perimenopause comprehends oral contraception, progestins and HRT. In menopause, low dose HRT and tibolone. In postmenopause, raloxifene and bisphosphonate. Topical estrogen treatment is given in case of vaginal dystrophy.

Conclusions

Sexual hormones, in particular estrogens, are important pathogenetic factors for autoimmune diseases. Therefore, for women in menopause and diagnosed with autoimmune diseases, HRT can cause a worsening or a relapse of the disease.

As a matter of fact, HRT seems to exert a protective role against rheumatoid arthritis.

The issue is more controversial when it comes to HRT associated to patients with SLE. In this case, HRT seems to increase the risk of weak to moderate relapses of the disease, but not of a severe relapse.

When prescribing HRT, possible risk factors for thrombosis, cardiovascular pathology or osteoporosis need to be taken into consideration. These risk factors can often be identified in women diagnosed with autoimmune diseases because of the frequent use of corticosteroids, lipid profile alterations or positive antibodies to antiphospholipids.

For women in menopause and women with autoimmune diseases alike, HRT is advisable only for the treatment of hot flushes and not for other disorders such as the prevention of fractures due to osteoporosis.

Generally speaking, HRT is safe to treat severe vasomotor symptomatology in women in menopause diagnosed with inactive autoimmune disease. HRT can be given at low dose of transdermal estrogen associated with a natural progesterin for the shortest possible period of time and with negative thrombophilic screening.

For patients who have contraindications to HRT, it is possible to prescribe other medicines to treat vasomotor symptoms like SSRI antidepressants, clonidine, progesterone, tibolone or natural substances rich in isoflavones and sage leaf extracts. Other menopausal disorders can be treated as follows: transdermal testosterone is apt to promote sexual desire and increase sexual function; topical estrogens are suitable for menopause-related vaginal dryness, diet and physical activity; SERMs and bisphosphonate lower the risk of developing osteoporosis.

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Hormone replacement therapy and autoimmune diseases

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