

HORMONE REPLACEMENT THERAPY IN MENOPAUSE

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ABSTRACT

The menopause is understood like a menstruation cease, because of sudden fall in hormone production. Generally, the symptoms at this stage are heat waves, lack of vaginal lubrication, loss of skin elasticity, hormonal changes, intensification of bone decalcification and reduction of libido. In order to alleviate these symptoms there are Hormone Replacement Therapies (HRT) that use synthetic drugs as estrogen and progesterone and/ or phytoestrogens as isoflavones. However, must be analyzed each person and the purpose of treatment. The prescription medications should be made based on the risks and benefits for the patient, aiming to improve the quality of life and relief of discomforts caused by hormonal lack.

KEYWORDS: Menopause, hormone replacement therapies, estrogen, progesterone, isoflavone.

1. INTRODUCTION

Throughout the life cycle, women are faced with a series of hormonal changes, with menarche, first period, the representative mark of the beginning of the reproductive period and menopause, with the stop of menstruation, the end of this period. Menopause is the result of disruption of production of ovarian follicles as a result of a sharp decline in the production of female hormones, which takes place between 40 and 50 years^{1,2}.

Regarding to their origin, menopause may occur in two forms: natural menopause divided into early and late and the artificial divided into surgical and radiotherapy chemotherapy³.

Twelve months prior to the experiment are referred to as perimenopause, which is the period of change between reproductive and non-reproductive phase. This period is the first of three phases of menopause, also called premenopausal or perimenopausal then has properly menopause, and then, post-menopausal^{4,5}.

The lack hormonal featuring menopause induces prevalence of symptoms such as hot flashes, decreased vaginal lubrication, reduction in the elasticity and stiffness of the skin, changes in mood, loss enhancement of bone calcification as well as reduction of libido⁶.

In order to alleviate these symptoms, there Hormone Replacement Therapies (HRT), using synthetic drugs

such as estrogen and progesterone and/ or phytohormones such as isoflavones. To do so, each agency and the purpose of treatment should be considered⁶.

The inclusion of healthy habits in everyday life through physical exercise, balanced diet and entertainment with activities that enhance the quality of life are also important points that may reflect on healthy aging and possibly in a less discomfort with menopause⁷.

Therefore, this study aimed to address the hormone replacement therapies that make use of synthetic hormones and phytoestrogens aimed at mitigating the symptoms of the menopause, it was necessary to distinguish the phases that compose it, set the menopause and its types and present prominent symptoms.

MATERIAL AND METHODS

This study was based on a literature review, through the survey and consultations on scientific sites like: library Scientific Electronic Online (SciELO) and Latin American and Caribbean Literature on Health Sciences (LILACS), using keywords like: menopause, hormone replacement therapy, estrogen, progesterone and isoflavones.

In search of material were taken into considering the articles that contained a broad approach to the use of hormone replacement therapy in menopause, as well as the definition of the symptoms and stages of their.

2. LITERAURE REVIEW

Menopause is composed of three stages: perimenopause, menopause and postmenopause.

Menopause, also known as perimeno-break or pre-menopause is diagnosed by menstrual irregularity present in the 12 months leading up to menopause⁵.

It is characterized as a period in which a decrease occurs in the production of hormones, estrogen and progesterone, due to the decreased ovarian activity. Rocha (2010)⁸ stated that with the disappearance of ovulation and corpus luteum formation in the uterus, thereby re-

ducing the reservoir of follicles in the ovaries occur making the body unable to developing embryo in its early stages, marking the transition from premenopausal for senescence⁹.

Menopause is considered as the period perimenopause (two to five years before the last menstrual period) until one year after the end of menstrual cycles⁹. This stage can be characterized by hypoestrogenism, leading to prevalence of symptoms such as hot heat, irritability, sweating, headache, decreased sexual desire, anxiety, night sweats and other¹⁰.

Already menopause itself is understood as the cessation of menstruation. Results from a series of changes that occur in the ovary, since the decline of gonadal function to the depletion of follicles, leading to a disturbance in the synthesis of estrogen and progesterone, characterizing the end of the reproductive period of woman. Generally, this phase takes place at around 45 to 55 years of age^{5,11}, followed by one year of amenorrhea¹¹. Menopause can, in some cases, be diagnosed as menstrual or even as an exacerbation of vaginal blood flow and may lead to irregularities frames hemorrhage⁹.

Finally, we have the post-menopause, which covers the period of one year after amenorrhea, and in some cases, prevails in later years. The same can be divided into early post-menopausal corresponding to the first five years of menopause and late post-menopausal women who are following the end of the recent post-menopausal ten years. At this stage the woman should be aware of the changes that may occur in your body, being the common prevalence of osteoporosis due to extremely low levels of estrogen, as well as the onset of heart disease^{3,12,13}.

Types of menopause

Regarding its origin, menopause may be natural or artificial factors of current³.

Natural menopause occurs spontaneously according to the female physiology, without interference from extrinsic factors, may present early or late way³.

Early menopause can occur around 40 years old going on due to the increase of the hormones FSH and LH, and autoimmune processes that would completely inhibit the functioning of the cells of the ovary. Thus, there is an early ovarian failure, and hence the depletion of ovarian follicles, leading the last menstruation. During this period the increase in LDL can occur, as well as the onset of osteoporosis and insomnia³.

There are reports that smoking is seen as a factor that favors the anticipation of menopause, due to hypoestrogenism caused by the same. Beyond the early menopause, tobacco use may enhance the development of osteoporosis and the onset of cardiovascular disease¹⁴.

On the other hand, late menopause is taken as a rare and occurs when the last menstruation occurs at about

age 55, in which case the probability of diagnosis of breast cancer and endometrial is increased due to prolonged hormonal stimulation⁴.

Artificial menopause as their name suggests, are cases which is caused by menopause artificial factors, namely the female body is subjected to changes that induce menopause. There are several reasons that lead to this event and can be divided into surgical, chemotherapy, radiotherapy and transient³.

Surgical menopause is caused by performance of an oophorectomy, consisting of the removal of the ovaries or a hysterectomy, the uterus is removed, the extinction occurring in the production of sex hormones and consequently making menopausal women³.

Regarding chemotherapy menopause, it is acquired as a result of exposure to substances used in chemotherapy³.

Already radiotherapy menopause is caused by exposure to radiation due to neoplastic treatments arising from the use of synthetic hormones⁴.

Finally, the temporary menopause from the use of medications for treatment of fibroids and endometriosis, that interfere with the natural physiology, thereby inhibiting the action of GnRH hormone producing the FSH and LH, and as a result of cessation of hormone production^{3,15}.

Hormone Replacement Therapy (HRT)

As a consequence of hormonal changes from the female physiology, all women at some point in their life cycle through menopause will thus suffer from the discomforts arising from same.

Whereas life expectancy in Brazil has increased from 70 years in 2000 to 74 years in 2013, according to IBGE, it is estimated that Brazilian women spend more than a third of his life in postmenopausal consequently will have a period of hormonal shortage prolonged. Thus, there is need to use treatments that aim to provide better quality of life by relieving the discomforts caused by this hormone lag^{16,17}.

To assist in alleviating the symptoms, there HRT composed of synthetic hormones and/ or phytoestrogens.

HRT makes use of synthetic hormones like estrogen and progesterone, has been an increasingly acceptable alternative among women. The use of estrogen during this period will lessen vasomotor discomforts and act in controlling bone density. On the other hand, progesterone associated with estrogen may contribute to the protection of the uterine lining, preventing the prevalence of endometrial carcinogenesis. However, it should be considered the treatment time and the characteristics of each patient. According to the Pan American Health Organization (PAHO) should opt for a quick therapy does not exceeding five years and preferably at low doses¹⁸.

As with any other drug treatment, the patient will be

subject to the incidence of side effects. Clinical studies conducted by the Women's Health Initiative (WHI) show that the use of synthetic-based estrogen and progesterone increase the possibility of breast cancer and thromboembolic diseases¹⁹.

There are controversies regarding the use of this type of treatment because of side effects previously mentioned above, with this many patients end up anticipating the end of treatment, or adhering to therapy that uses phytoestrogens such as isoflavones, since they have similar effects to estradiol. However, if treatment is appropriate taking into account factors such as the route of administration, the genetics and physiology of each organism always happen through medical care, the benefits may outweigh the risks²¹.

Synthetic hormones

Hormones are substances essential for the regulation and operation of all human physiology processes are involved in the growth, reproduction, and metabolism. Over the years, the female body naturally undergoes wear, occurring some transformations such as hormone deficiency when entering menopause. To overcome this lack, HRT has been widely used. The same is the use of synthetic hormones, or artificially synthesized substances, which are aimed at replacing natural hormones and reduction of climacteric discomfort arising as vasomotor symptoms, vaginal dryness, osteoporosis and other^{22, 23}. Among the synthetic hormones most used, highlight the estrogen, progesterone, and tibolone.

About the estrogen synthesis in human body is controlled by means of stimulation of the hypothalamic/pituitary axis. Initially the hypothalamus will stimulate the pituitary to release FSH in the blood stream, in turn, FSH contact promotes ovarian hormone release and circulating estrogen production when it reaches the appropriate level, there occurs the release of LH thus the formation of the corpus luteum and the synthesis of other hormones. However, over the years this cycle becomes irregular²⁰.

After the cessation of menstruation hypoestrogenism is inevitable because the synthesis of estrogen decreases gradually and one way to restore this deficiency is the use of synthetic hormones. Estrogen is present in the execution of many physiological processes. It is a substance of great importance in the treatment of menopause can act in mitigation of vasomotor symptoms and preventing bone loss through increased mineral absorption. Can still be used in cardiovascular problems, inhibiting platelet aggregation, acting in decreased glucose levels and promote increased vascularity and collagen synthesis in the skin, it is essential to restore strength, elasticity, decreasing the incidence of wrinkles. Its deficiency can cause urogenital system boards urinary incontinence^{17, 10}.

Therapies that use of estrogen and progestin are the most common. This because the use of estrogen alone can cause a number of severe side effects such as endometrial cancer²¹. Some randomized studies have shown that this type of cancer in the seventh place among the existing neoplasms, mainly in developed countries²⁴.

As early as concerns the tibolone, clinical studies showed that the same, in contact with the blood have the capability to provide estrogenic effects, with significant results in controlling hot flashes, skin elasticity, osteoporosis, and may act in reducing headache. Because of its androgenic property, has been an increase in testosterone resulting in improvements in the sexual realm, by controlling disturbances of libido and urogenital atrophy, and eventually his progestin therapy function provides protection by preventing possible uterine cancer⁶.

Risks and benefits of HRT with synthetic hormones

Risks:

Prevalence of breast cancer: studies indicate that women who use HRT using estrogens have predisposition disorderly proliferation of cells due to the stimulation of mammary glands, which leads to the same, and consequently, development of tumors. This type of cancer is usually diagnosed in premenopausal, which occurs around the age of 50. Chemotherapy and surgical procedures are some of the alternative treatment in order to prevent an increase in neoplasia^{25, 26}.

Venous thromboembolic disease: the risk of venous thromboembolism is increased among HRT users, since the effects of estrogen in the clotting mechanism may contribute to or be responsible for a generalized hypercoagulable state. Oral estrogens affect the synthesis of clotting factors by a hepatic first pass. Studies indicate that use of estrogen for transdermal, may be associated with a lower risk for thromboembolic events compared with oral estrogen, since by not transdermal occurs first pass metabolism. However, randomized clinical trials are needed to better characterize the different effects of estrogens by mouth not in risk of events²⁶.

Endometrial cancer: the isolated use of estrogen can promote the emergence of endometrial cancer, so women who have or have a history of uterine endometrial carcinoma are prone to develop this disease, and should opt for the concomitant use of estrogen and progesterone, ie, the separate administration should be exclusive to patients hysterectomy^{27, 28}.

Systemic lupus erythematosus: studies indicate that HRT with estrogen may contribute to the spread of this disease and aggravation of the case, so its use is contraindicated in patients with systemic lupus²¹;

Ovarian cancer: it is considered the most common type of cancer among women and the difficulty of diagnosis, usually when discovered, is already at an ad-

vanced stage. Long-term use of estrogen leads to the formation of neoplasms, as well as their residual effects favor the propensity of the disease^{27,29}.

Liver Disease: in patients with acute liver disease is contraindicated hormone therapy. Patients with chronic liver dysfunction also should not receive therapy is particularly orally. On the other hand, some studies using estrogen not orally showed no adverse effects in patients with primary biliary cirrhosis and chronic hepatitis cases of active²¹.

Benefits:

Alleviation of hot flashes: coming from estrogen deficiency, heat waves are also intensified by extrinsic factors such as smoking, alcohol. Sa *et al.* (2006)³⁰ demonstrated that the upper body like the arms and face, are the hardest hit with hot flashes from that stage, so the hormone replacement therapy helps in easing this discomfort³¹.

Control of drying of the vaginal mucosa: decline in estrogen leads to reduced synthesis of sebaceous glands, which are responsible for vaginal lubrication, thus, there is minimal discomfort and bleeding and trauma. Hormone reposition can normalize levels of this substance and restore the functioning³¹.

Osteoporosis: hypoestrogenism resulting in decreased calcium absorption and in the synthesis of calcitonin, so the risk of fracture is enhanced during menopause. Certain studies highlight the efficacy of the HRT in relation to reduction of fractures due to osteoporosis because these therapies, whether used with or associated with estrogen-progesterone, can save for increasing intestinal calcium absorption or by increasing the renal conservation thereof. In addition, estrogen may have a direct effect on the function of osteoclasts, reduce bone loss and to a limited extent, reverse the onset of osteoporosis. However, studies indicate that the results are perceived only during treatment, and with the cessation of estrogen therapy, has the deficiency in calcium reabsorption again¹⁷.

Skin changes: over the years, the skin undergoes some modifications. For stiffness and elasticity, the estrogen treatment provides significant results in the regeneration of the skin due to increase of tissue cells and collagen production, thus restoring the integrity and improved expression marks³².

Phytoestrogens

In order to reduce the discomfort caused by menopause natural substances that contain phytoestrogens can be used³⁴.

Phytoestrogens are nonsteroidal diphenolic compounds, which are estrogen-like structure. Are capable of binding to the estrogen receptor ER α that can be found in the uterus, liver, kidney and breast tenderness and ER β

estrogen receptors present in prostate, ovary, testes and pituitary. Phytoestrogens are divided into three classes: lignans, isoflavones and the cumestanos, the latter being the most common phytoestrogen^{34,35}.

Isoflavones are phenolic compounds whose biosynthesis of the phenylpropanoids pathway stems. Its molecule is similar to estrogen, however, their functionality is less intense. It is found in higher concentrations in the legumes especially soybean (*Glycine max*) which is connected to sugars and beta-glicosídeos. Soy is extremely important as active substances as genistein and daidzein, which are subtypes of isoflavones³⁶. To that isoflavones are absorbed by the body must be in the form of aglycones, because only then managed to cross the plasma membrane and exert its effect. It is noteworthy that the absorption occurs in a dose-dependent, ie the concentration rises proportionally to the amount consumed. During its use is contraindicated antibiotics, as they can interfere with the absorption of the same³⁵.

Genistein is an isoflavone component, which alone or combined with daidzein may inhibit the growth of cancer cells. The daidzein exerts this effect only when combined with genistein, its mechanism of action includes the inhibition of enzymatic activity of thyroxine kinase, ribosomal kinase, DNA topoisomerase controlling the uncontrolled growth of cells. Genistein may also have vasodilating action, inhibit oncogenesis and angiogenesis and surveys indicate an improvement in lipid profile from genistein and daidzein binding in liver receptors favoring the catabolism of LDL cholesterol^{20,36,37}.

Recent studies regarding isoflavones results indicate, that many flavonoids exhibit inhibitory activity on P-glycoprotein-mediated transport. Among these flavonoids are included genistein. Knowing that the digoxin and quinidine are substrates of this protein, which has the same actions as limiting oral bioavailability, facilitating the biliary excretion and renal clearances of these drugs, we can conclude that the interaction between isoflavones and these drugs may induce cardiac a picture of intoxication increased serum concentration of the latter³⁶.

Isoflavones may also generally operate in the intensity of hot flushes resulting from estrogen decline, having antioxidant activity, for inhibiting free radicals, provide satisfactory results in bone formation preventing the onset of osteoporosis, and in order to have a vascular protective action³⁸.

It is recommended that the intake of 45 mg/ day, however studies indicate the use of up to 160 mg/ day without adverse effects³⁶.

Isoflavones are presented as an alternative between prescriptions where not exhibit higher probabilities of incidence of breast cancer due to decreased risks of this treatment provides, but the alleviation of menopausal

symptoms will occur in smaller proportions²⁷.

Besides soybean, plants may be other sources of phytoestrogens. Among them stand out the Primrose (*Oenothera biennis*), the Licorice (*Glycyrrhiza glabra*), the Cimicifuga (*Cimicifuga racemosa*), the Dong quai (*Angelica sinensis*), the Ginseng (*Panax ginseng*) e o Trefoil of the meadows (*Trifolium pratense*).

Regarding the Primrose, its seeds are rich in oils containing linolenic acid and linoleic acid. There is evidence that its oil reduces the incidence of hot flashes during the night in menopausal women, and increase calcium absorption by the intestine, thereby increasing bone deposition thus preventing osteoporosis. Its oil is also much used in cases of mastalgia and its use does not induce the formation of nodules. It can also be used to decrease the intensity of symptoms like hot flashes and in the control of LDL and HDL³⁶.

The Licorice (*Glycyrrhiza glabra*) has active substances in its composition as glycyrrhizic acid and some isoflavones. Its can act in reducing estrogen levels also have significant results in increased progesterone. The recommended daily dose is 380 mg and should be avoided by hypertensive, as it may contribute to increased blood pressure, as it has the ability to retain sodium. Hypokalemia can further increase, and therefore its use simultaneously with the digoxin and loratadine should be avoided due to the risks of intoxication by these drugs³⁶.

In the case of Cimicifuga (*Cimicifuga racemosa*) Sousa, *et al.* (2006)³⁶ has as main active substances the isoflavones, formononetin and triterpenic terpenoids. Emphasize its possible action on vaginal atrophy, besides relieving hot flashes and reduce the release of LH. The recommended daily intake is 20 mg daily. Their use should be avoided in combination with the use of anti-hypertensive agents, for Cimicifuga can cause a sudden fall in blood pressure³⁹.

Already *Angelica sinensis*, popularly known as Dong quai, participates in the regulation of the hormone estrogen, which may alleviate hot flashes and vaginal dryness. In addition, has anti-inflammatory action, prevent thrombus formation, improves blood flow contributing to a good cardiac function, and may serve as a hepatic protector. Moreover, it can also have power, anti-hypertensive, antispasmodic, antibiotic action to reduce dysmenorrhea, amenorrhea and hypermenorrhea. The recommended dose ranges from 300 to 500 mg once to five times a day, and should always be taken with food^{36,39,40}.

The Ginseng (*Panax ginseng*) acts on the immune system providing greater resistance to external aggressors. Has stimulating action promoting increased physical and mental vigor. Also contributes to hormonal balance, thus there is a control on behavioral oscillations providing better interaction with the social circle. Can be effective in relieving vaginal dryness and pain during intercourse.

Also has the effect, control the menstrual disorders. However, the appearance of estrogenic effects in women were reported in pre and postmenopausal inducing breast pain and metrorrhagia in the sequence of use of Ginseng. Should avoid their combined use warfarin because it can interfere with the action of this drug, thus decreasing the effect of inhibiting the formation of blood clots^{36,41}.

The Trefoil of the meadows (*Trifolium pratense*) has as main active substances isoflavones and coumarin derivatives. Promotes relief of hot flashes, decreased vascular resistance, thereby lowering blood pressure. Studies report that can be an alternative for women who are prone to breast cancer, because it may decrease or stop the proliferation of breast tumor cells. Due to the presence of coumarin derivatives may decrease the blood coagulation time, so its use is contraindicated in patients who take anticoagulants and antiplatelet agents, it can cause increased bleeding time and consequently hemorrhaging. The maximum dose is 500 mg. Concurrent use with digoxin should be avoided as it may enhance its effects, increasing the risk of toxicity of this drug³⁶.

3. CONCLUSION

At some stage of a woman's life, as a result of natural aging, decreased production of hormones occurs, resulting in menopause.

The hormone replacement therapies, which use synthetic hormones, help to normalize hormone levels and to mitigate the perceived symptoms during menopause. However, you should take into account the characteristics of each patient, because of the risks and benefits that it can bring.

Another option are existing therapies that make use of phytoestrogens such as isoflavones. This therapy may provide relief of symptoms arising from the menopause, causing fewer side effects, among both its effect on the symptoms may be less than shown by the use of synthetic hormones.

Prescriptions should be made based on the risks and benefits for each patient, aiming to improve the quality of life for menopausal women, alleviating the discomforts caused by this hormone lag.

Physiological changes in the female body are inevitable and menopause consists of the phases to be lived according to human chronology, therefore, studies on the subject contribute to demystify and help in understanding the changes experienced.

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