



A PHARMACY CONTINUING EDUCATION PROGRAM

W-F Professional Associates, Inc. 400 Lake Cook Rd., Suite 207 Deerfield, IL 60015 847-945-8050

October 2009 "Review of HRT" #707-000-09-010-H01-P



THIS MONTH
"Review of HRT"

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It's been about 3 years since we last addressed hormone replacement therapy. This is one of those topics that repeatedly appears high on your list of requests. Our goals are to discuss therapeutic options, and to provide information that may be shared with patients. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings. **The program ID # for this lesson is 707-000-09-010-H01-P. Pharmacists completing this lesson by October 31, 2012 may receive full credit.**

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

The objectives of this lesson are such that upon completion the participant will be able to:

1. Define the term "hormone," and relate their importance.
2. Describe sequence of physiological events that lead to menstruation.
3. Comment upon the role of HRT in treating osteoporosis.
4. List the adverse effects of HRT.
5. Discuss the usefulness of MHRT.

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INTRODUCTION

Hormones are chemicals released in very small quantities by certain cells, and they allow the body to perform various physiological functions such as growth and development, metabolism, sexual desire, mood, activation or inhibition of the immune system and reproduction. All multicellular organisms, including plants, produce hormones (phytohormones). Even though hormones are present in small amounts, they are potent and capable of producing significant changes in cells as well as in the entire body. Any reduction or overproduction of these chemicals can result in serious disorders and changes in body functions.

Hormones are body messengers that carry signals from glands to cells in order to act as a catalyst for certain chemical changes that take place in the body. Hormones are manufactured in glands and travel in the bloodstream to reach their targets. Once the intended cell is reached, the hormone binds with the protein of specific receptors to activate a signal transduction mechanism that results in a cell-type specific response. Thus the receptor of the target cell can only be activated by a specific hormone. Synthesizing cells for hormones are found in particular endocrine glands such as the thyroid, ovaries and testes. Endocrine hormones are secreted directly into the bloodstream, whereas exocrine hormones are released into a duct that delivers the hormone to the bloodstream, or they are transported from cell to cell by diffusion.

In general, hormones exist in two forms: **steroids and peptides**. **Steroids**, which are made of cholesterol, include sex hormones. Such hormones, which are produced by ovaries and testes, are responsible for sexual maturation and reproduction. If the body is not producing enough sex hormones such as estrogens, progesterone and testosterone, then they can be supplemented or replaced, hence the term hormone replacement therapy (HRT). **Peptide** hormones differ from steroids in that they consist of long chains of amino acids (protein). Growth hormone and insulin are examples of peptide hormones.

The primary hormones of the female reproductive system are estrogen (estradiol) and progesterone, both of which are steroids secreted by the ovaries. Estrogens are responsible for the development of the female sexual characteristics such as breasts, broadening of the pelvis, growth of pubic and axillary hair and increase in the formation of adipose tissue. In addition, they assist in the monthly changes that take place in the uterus in preparation for pregnancy. Progesterone plays an important role in the menstrual cycle and pregnancy.

Estrogen is released from the ovaries under the influence of follicle-stimulating hormone (FSH), which is controlled by the gonadotropin releasing hormone (GnRH) produced by the hypothalamus. High levels of estrogen in the blood will trigger a negative-feedback mechanism resulting in suppression of the release of (GnRH). Progesterone is released by luteinizing hormone (LH), which in turn is stimulated by GnRH. Like estrogen, high levels of progesterone act by the same negative feedback mechanism. Both estrogen and progesterone play major roles in the menstrual cycle initiation and cessation. Approximately every 28 days, a healthy female experiences the vaginal flow associated with disintegrated endometrial tissue. The physiological process that results is known as menstruation. After a menstrual cycle ceases, a new ovarian follicle begins to develop. This development is accompanied by a gradual increase in the amount of estrogen as well as in the thickness of the endometrium. The increase in LH blood levels results in the development of an ovum (egg) within the follicle. After about two weeks from day one of the menstrual cycle a surge in the level of LH occurs resulting in the release of the egg (ovulation) into the fallopian tube. The empty ovarian follicle becomes corpus luteum which secretes progesterone. If the released egg does not meet a sperm, fertilization will not occur. The rising level of progesterone will inhibit the release of GnRH through the negative feedback mechanism and in turn inhibits further release of progesterone. Once progesterone level declines, the corpus luteum begins to degenerate followed by disintegration of the endometrium. On day 28 a new cycle begins. The vaginal discharge usually contains blood, disintegrated endometrial cells and gland secretions which contain an enzyme that prevents blood coagulation. The amount of discharge varies from one patient to another and from month to month, but the average is 30 to 40 ml. Menstruation ceases during pregnancy and lactation.

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October 2009

MENOPAUSE

The occurrence of the menstrual cycle continues throughout the reproductive years. However, between the ages of 45 to 55, the ovarian follicles become less responsive to the stimulation of FSH and LH. The weight of ovaries decreases to about one-third of that before commencement of menopause. This is usually accompanied by a gradual decline in the secreted amounts of estrogen resulting in irregularities in menstruation, which gradually ceases.

The physiological cessation of menstrual activity is termed menopause (Greek: menos, meaning month; and pausis, meaning cessation). From a clinical point of view, menopause is a physiological event that occurs after 12 months of absence of menstruation. Premature ovulation may occur as a result of radiation exposure, and use of chemotherapeutic agents. Genetic factors may play a role in triggering the onset of menopause. Tobacco smoking appears to hasten the onset of menopause by about 2 years. This may be due to the effect of nicotine on the ovaries as a result of acceleration of hormonal metabolism. Hysterectomy may accelerate the start of menopause even in the presence of ovaries.

It has been estimated that menopause occurs in 25% of women by age 49, in 50% of women by age 50, 75% of women by age 52, and 95% by age 55. The time of transition to menopause, through which the amount of estrogen is diminishing, is termed climacteric. After menopause, the main estrogen found in the circulation is estrone, which is less potent than estradiol, and is usually formed as a result of conversion of estrogen androstenedione. The conversion process occurs under the influence of the enzyme aromatase, which is abundant in fatty tissue and the liver. The level of this enzyme increases with age as more fatty tissue is accumulated in the body. Prior to menopause, the daily production of estrone and estradiol is 80 – 300 mg and 80 – 500 mg respectively. This compares to 40 mg of estrone and 6 mg of estradiol postmenopausally. The estradiol found in circulation after menopause is derived from the conversion of estrone to estradiol. Another hormone that is affected during climacteric is progesterone. During this time, progesterone level begins to diminish and eventually becomes negligible.

SYMPTOMS

Hot Flashes: Menopause is usually accompanied by symptoms which may range from mild to intolerably severe. However, they may be asymptomatic in some women. The symptoms which usually occur during climacteric include vasomotor symptoms such as flashes as well as night sweats, weakness, depression, insomnia, weight gain, urinary incontinence, fatigue, irritability and nausea. Furthermore, reduction in estrogen levels may lead to osteoporosis, and a decrease in the size of the reproductive organs and breasts. The vaginal mucosa becomes thin, dry, atrophic and smaller in size. Vasomotor symptoms are experienced by 50 to 85% of women during the climacteric period. They are characterized by a feeling of warmth over the chest, neck and facial areas that may appear as red flushing. Hot flashes usually begin at the center of the body as a sensation of heat that spreads toward the head causing flushing of the neck and face. These episodes may last from a few seconds to 30 minutes. Increased pulse rate, shallow breathing and sweating, followed by chills may be experienced. The patient complains of increased sweating especially at night. Episodes may emerge prior to the last menstrual cycle experienced, but occur most frequently during the two years after the beginning of menopause, and gradually diminish over time. The vast majority of individuals complain of experiencing these symptoms for longer than one year. About 25% of the sufferers are affected for longer than 5 years.

Estrogen therapy may provide symptomatic relief of hot flashes. The patient may begin with a low oral dose of 0.3 – 0.45 mg of estrogen. Estrogen–progestin therapy may be attempted for women with an intact uterus. Transdermal estradiol may be used as an alternate. A recommended starting daily dose is 0.025 or 0.05 mg. The dose may be increased to 0.1 mg/day only if the symptoms persist.

Atrophic vaginitis: As estrogen begins to decline, menopausal patients may experience symptoms associated with atrophy of the genitourinary tract. Additionally, weakened defense mechanisms, especially vaginal pH, may occur. The pH of the vagina depends on cervical secretions and on the presence of normal vaginal microbial flora, particularly Döderlein bacilli, which help convert the glycogen in the vaginal epithelium to lactic acid. This keeps the pH strongly acidic. The pH in a normal individual is acidic and ranges from 4.5 to 5.0. During menopause the vaginal pH may reach 6 to 8, and thus predisposes the menopausal patient to vaginal fungal or bacterial infections. The acidity during the reproductive years provides protection against infection. Following menopause, the vaginal epithelium becomes thin, and as a result, the level of glycogen within the vaginal wall decreases. This is followed by reduction in the formation of lactic acid, the substance responsible for acidifying the vaginal environment. Thus, the vagina becomes vulnerable to infection. The thinning of the vaginal wall results in symptoms such as inflammation, burning, watery vaginal discharge, itching, bleeding and painful intercourse. Moreover, atrophic changes in the thickness of the urethra and urinary bladder may lead to nonbacterial urethritis, which is characterized by dysurea (painful urination), frequent and urgent urination and nocturea (frequent urination at night). Local (intravaginally) or systemic estro-

gen therapy may provide symptomatic relief of genitourinary atrophy. Daily application of intravaginal cream for one to three months, and then intermittently as needed, may be recommended. Vaginal tablets containing 2 mg of estradiol may be used daily for two weeks, then twice daily. A vaginal ring that slowly releases 7.5 mg of estradiol daily for 90 days may be used.

Osteoporosis: Osteoporosis is a disorder characterized by low bone density and microarchitectural deterioration of bone tissue resulting in fragility and vulnerability to vertebral and non-vertebral fractures. This leads to bone fragility and increased risk of bone fracture. Bones are either cortical or cancellous (spongy, lattice-like). The cortical bones are dense and located in the outer layers of the skeleton, whereas the cancellous bones are situated in the interior portion. The long bones of the skeleton consist mostly of cortical bones except for their ends which are mainly cancellous. A continuous remodeling process in bones occurs as a result of a balance between osteoblasts, which helps in rebuilding of bony surfaces, and osteoclasts, which resorb bone. The remodeling process is a cycle of destruction (breakdown) and renewal (formation).

During childhood and early adulthood, the rate of bone formation is equal to the breakdown. The net result is there is no bone loss. Bone mass reaches its highest level at 30 to 35 years of age. After this age, cortical bones begin to decline by up to 0.5% each year. At menopause, this decline in cortical bone mass accelerates to reach 2 to 3% yearly. This decrease occurs as a result of diminished concentration of estradiol. Cancellous bone loss begins during the third decade of life with yearly decrease of about 0.6 to 0.8 % each year.

Osteoporosis is a major public health problem that affects over 11 million people in the U.S. Obviously, the incidence increases as patients become older. The frequency of fractures also increases with age. Over 1.5 million osteoporosis related fractures occur each year. Most of these are in the vertebrae, distal radius and hips. It has been estimated that 40% of Caucasian females over 50 years of age will suffer fractures of the spine, distal forearms or hip during their lifetime. Women who experience hip fractures have a 12 to 20% higher mortality rate. Annual cost in the U.S. of osteoporosis related fractures exceeds \$14 billion. To reduce future risk of developing osteoporosis, the patient should be advised to maximize the peak bone mass and prevent bone loss. The intake of adequate amounts of Vitamin D, which assists in calcium regulation, is recommended. Daily requirements of Vitamin D range from 200 – 600 IU. It is also important to ensure that the patient receives about 1,000 mg of calcium per day, whether this amount is through diet or in the form of a supplement.

HORMONE REPLACEMENT THERAPY

Since menopause is a normal physiologic phenomenon of aging due to reduced estrogen levels, and is associated with unpleasant symptoms and often damaging to health, it is necessary to reestablish adequate levels of estrogen in blood.

Quality of life, as well as mortality caused by estrogen and progestin deficiency may improve following hormone (estrogen) replacement therapy (HRT). This approach assists in preventing osteoporosis, genitourinary atrophy, and vasomotor symptoms of menopause. Hormone replacement therapy is the mainstay for treating postmenopausal symptoms. The main objectives of HRT are to improve the quality of life and to prevent or reduce the risk of emergence of disorders associated with menopause. The rationale behind the use of HRT is to reestablish an adequate level of estrogen, thereby relieving the climacteric symptoms of menopause. It is estimated that as many as half the postmenopausal women in the U.S. use one or more forms of estrogen substitute (i.e. diethylstilbestrol), synthetic estrogens (i.e. ethinyl estradiol) or micronized estradiol. The most widely used one is conjugated estrogen, which consists of estrone sulfate and multiple other equine estrogens. In addition to providing relief from climacteric symptoms, there is evidence to indicate that it can prevent osteoporosis and exerts positive effects on calcium balance and bone density. It has been shown that women given HRT have experienced lesser incidence of bone fracture.

Dosing information must be thoroughly explained to the patient. For long-term therapy, HRT should be administered at the lowest effective dose. The patient must be evaluated every year to determine the need for continuation of medication. Prolonged HRT, along with the concurrent use of progestin for at least 10 to 14 days of each cycle, may be attempted in postmenopausal patients with an intact uterus. This tends to decrease the risk of development of endometrial hyperplasia and endometrial carcinoma. Estrogen is usually given alone for the first 15 days, and a combination of estrogen and progestin for the remainder of the month. Other regimens involve the continuous administration of estrogen along with low dose continuous progestin. Additionally, HRT may be used on a cyclic or continuous basis. A patient may follow a cyclic regimen consisting of three weeks of estrogen and progestin concurrently

administered for the first or last 10 to 14 days of the three-week period. During the fourth and final week of the cycle, no medication is given. The dose of estradiol, as well as the frequency of administration and duration of use, varies from one individual to another depending on the medical problem for which the medication is taken or applied. Due to diminished production of estrogen in the immediate and post-menopausal years, the risk of development of osteoporosis is increased. It has been shown that starting HRT within the first five years of menopause, and continuing for at least 10 years, causes 50% reduction in incidence of hip fracture. To prevent bone loss, it is recommended that HRT is initiated immediately after menopause because there is an increase in the rate of bone loss in the first 3-6 years. Cessation of HRT may result in a rapid bone loss. This therapy should be continuous.

ADVERSE EFFECTS

A potential adverse effect of HRT is the increased risk of endometrial cancer. The risk after 5 years of estrogen use is believed to increase by a factor of 3.5. This risk seems to rise with increasing duration and dosage of estrogen.

The inclusion of progestin with estrogen has been shown to reduce the endometrium mitotic activity. The association of breast cancer with HRT has not been resolved. Some studies have shown that the use of estrogen in high doses and for prolonged periods (longer than 10 years) has increased the risk of breast cancer. Other studies did not indicate this finding in patients who used HRT.

There is no conclusive evidence to indicate that low doses of HRT in postmenopausal women contribute to an increase in the severity or incidence of thromboembolic disease, hypertension, atherosclerosis, myocardial infarction or stroke. Women on HRT should be instructed concerning the dosage and mode of administration. For long term use in post menopausal women, HRT should be used at the lowest effective dose. The patient should be evaluated every year to determine the need for continuation of therapy. Prolonged HRT, along with concurrent use of progesterone for at least 10 to 14 days of each cycle, may be attempted in post menopausal women with intact uterus. This tends to decrease the risk of the development of endometrial hyperplasia and endometrial carcinoma.

METHODS OF ADMINISTRATION

Estrogen occurs naturally or may be synthetically prepared. The oral route has been utilized for over 55 years. Today, a wide range of delivery systems are used allowing long term therapy to be designed for individual use. Estrogen may be administered orally, transdermally, intravaginally, intramuscularly or subcutaneously as implanted pellets. The most convenient routes are oral and transdermal.

Oral route: This route is the most common one. It provides adequate blood levels of estrogen and effective relief of symptoms. It is convenient, easy to stop, relatively inexpensive and has a short half-life. The main disadvantage is that only about 10% of the dose reaches systemic circulation due to the fact that it undergoes conversion to inactive metabolites in the GI tract, and because of first pass metabolism in the liver. Hepatic effects on orally administered estrogen may cause increased risks of gallstone formation, hypertension and hypertriglyceridemia.

The recommended average dose of conjugated estrogens is 0.3 to 1.25 mg daily; for esterified estrogens, the average dose is 0.625 to 1.25 mg daily; for estradiol, the average dose is 0.5 to 2 mg; and for estropipate the average dose is 0.75 to 6 mg. A combination of estradiol (5mcg) and norethindrone (1mg) in each tablet may be taken. In case of a missed dose, the medication should be taken as soon as possible, unless it is almost time for the next dose. In that situation, the missed dose should be skipped and the regular dosing schedule resumed.

Transdermal: Transdermal routes are available as patches or gels. Transdermal estrogen is absorbed directly from the skin, and enters the circulation in a regular continuous manner, thereby establishing estradiol-estrone ratios identical to those encountered by post menopausal women. Advantages of this route include: (1) estrogen avoids the influence of the GI tract and does not undergo first pass hepatic metabolism, (2) this route appears to have no effect on clotting factors, and no hepatobiliary effects similar to those encountered following oral administration. The main side effect of transdermal patches is irritation at the application site. However, it appears that matrix patches cause less adverse skin reactions than the reservoir patches. The use of transdermal patches enhances patient compliance.

One type of skin patch contains 0.025 to 1 mg estradiol, and should be applied to the skin and worn for a week. After that, the patch is removed and a new one is applied. The patches are applied weekly for three weeks. In the fourth week, the physician may not recommend applying a new patch. At the end of the fourth week, a new cycle should be repeated.

Another type of patch contains 0.025 to 1 mg. The patch is applied to the skin and worn for 3 weeks. The patches are applied twice a week for three weeks. During the fourth week, the physician may or may not recommend that a new patch be used. After the fourth week, the cycle is repeated. If the patient forgets to apply a patch when

due, the patch should be applied as soon as possible, provided it is not time for the next patch. In such a case, the missed patch should be skipped and a new schedule should be resumed. The application of a hydroalcoholic transparent gel containing 0.6 mcg of estradiol results in rapid absorption through the skin, causing therapeutically effective blood levels. This dosage form, which is available in Europe, is applied to the lower abdomen or arms and shoulders, and is allowed to dry for 2 to 3 minutes. It tends to relieve menopausal symptoms without causing changes in liver protein production.

Estradiol Implants: Estradiol implants (pellets) that contain 25 to 200 mcg of the hormone are implanted subcutaneously under local anesthetic. The drug is transported directly into the circulation, thereby avoiding first pass hepatic metabolism. The implanted pellet helps maintain adequate blood levels for 6 to 12 months, but may continue to release estrogen in small quantities for a longer time. Dose and its frequency are determined by weight of the patient and severity of the menopausal symptoms. Crystalloid implants possess the advantage of ensuring compliance, especially for forgetful patients. Frequent administration of these implants may lead to higher estrogen levels, especially since minimal metabolism occurs in the subcutaneous tissue. To prevent this from occurring, the implants may be administered once every 6 weeks and at a dose of 25 mcg. The drawback of this route is that minor surgery is required for insertion and removal, enhancing the risk of infection.

Vaginal routes: Vaginal estrogen therapy is usually intended to achieve local effects rather than systemic. Menopause can result in atrophic vaginitis and vulvar atrophy. Local estrogen therapy is effective in relieving these symptoms. Vaginal preparations utilized in estrogen delivery include cream, inserts (rings) and suppositories. Creams are applied with an applicator with marks indicating the amount to be inserted. For treating vulvar atrophy and atrophic vaginitis in postmenopausal patients, one-half to two grams of conjugated estrogen cream containing 0.3 to 1.25 mg are inserted into the vagina once a day or as directed by the physician. The cream should be used for only three weeks of each month. For estradiol vaginal cream, the dose is 200 to 400 mcg (2 to 4 grams of cream) once a day for one to two weeks, decreasing the dose by ½ over two to four weeks. After four weeks, the dose and its frequency may be reduced. The drawback of vaginal creams is the difficulty of measuring and administering the cream for elderly patients, especially those with poor sight. Additionally, the administration is messy and unpleasant, leading to poor compliance. Inserts are sustained – release delivery systems made of biologically inert-liquid polymer matrix, combined with pure crystalline estrogen. The insert or ring is about 55 millimeters in diameter, and is held in place during daily activities by the vaginal wall. The insert contains 2 mg, releasing 7.5 mcg every twenty-four hours continuously. The insert should be replaced every three months. Vaginal suppositories of estrogen, each containing 250 to 500 mcg, are inserted once daily or as directed by the physician.

MISCELLANEOUS THERAPY

Phytoestrogens: Phytoestrogens are delivered from plants, but structurally and functionally resemble estrogen synthesized by the body. These chemicals are widely distributed in oil seeds, vegetables and soy beans. There are a number of herbal products that have been utilized. However, recent research to determine the active ingredients, mechanism of action and potential clinical usefulness provided varying degrees of benefits of phytoestrogens for symptomatic relief of menopause. Safety studies for herbal products during pregnancy and lactation are inconclusive.

Soybeans and Isoflavones: The main active constituents in soybeans are isoflavones, which possess weak estrogenic activity ranging from 500 to 15,000 times less than that of estradiol. Reports indicate that soybeans may provide relief from menopausal hot flashes. Many nutritionists believe that the intake of soybeans in moderation is useful, but soy in large amounts can potentially be harmful. The isoflavones from soy may stimulate the thyroid glands. It appears that there is a higher risk of breast cancer in women who consume large and sustained quantities of soy.

Dong Quai: Dong quai has been used for premenopausal or menopausal hot flashes. Even though its efficiency for such therapy is questionable, its safety profile appears to be good.

Black Cohosh: Black cohosh is an herb native to Eastern North America. Native Americans used black cohosh for treating amenorrhea and menopause. Currently, black cohosh is used in the treatment of hot flashes, menopausal anxiety and depression. Extracts from the drug have been used in younger women suffering from hormonal deficits following ovariectomy or hysterectomy as well as juvenile menstrual disorders. Studies have shown that black cohosh has no significant effect on reduction of frequency or intensity of hot flashes.

Licorice Root: Several isoflavones have been isolated from licorice root and illustrate antioxidant activity. Of these, glabridin is the main constituent (11%) of an alcohol extract. Its lipophilicity and structure are similar to natural

estrogens. It has been shown that glabridin and its derivatives function as an estrogen agonist. At the present time there is no documentation to show the potential effectiveness of licorice root as an alternative to HRT.

HORMONE REPLACEMENT THERAPY IN MEN

The major male sex hormone is testosterone. This androgen steroid hormone is produced in the testes of males and in small quantities in the ovaries of females. It has been estimated that a human male body produces 40 to 60 times more testosterone than an adult female. Like men, the amounts of testosterone produced by women, even though smaller, are important in maintaining libido, bone density and muscle mass. Estrogen imbalance in men, i.e. higher level of estrogen than testosterone, causes a reduction in muscle mass, suppression of growth during teenage years, development of gynecomastia, increased vulnerability to prostate cancer, diminished libido, emergence of erectile dysfunction and increase in feminine characteristics.

Interstitial cells known as Leydig cells of the testes are responsible for the release of testosterone. Usually, the testes produce 4-7 mg of testosterone per day. Very little amounts are produced prior to puberty. However, during and after puberty there is a considerable increase in the secretion of testosterone. Production of testosterone decreases rapidly after the age of 50. The decrease reaches 20 to 50% of peak level by age 80. Testosterone deficiency is common. The incidence of testosterone deficiency among men who are obese or suffer from diabetes or hypertension is twice more frequent than healthy persons. The hormone is responsible for the development of sexual male characteristics, as well as general health and prevention of osteoporosis. Moreover, it facilitates protein synthesis and in an increase in size of body tissues that contain androgen receptors. This anabolic reaction results in muscle mass and strength, maturation and increased bone density. The changes in sexual characteristics include maturation of the sex organs, prostate, formation of the scrotum after birth, deepening of the voice as a result of vocal chord thickening, hair growth on the face and axilla, increased muscle strength and mass and increase in height and increased male libido. Moreover, testosterone is responsible for the development of sperm. Chemically, testosterone is a derivative of cholesterol. It is reduced to 5 α -dihydrotestosterone by the cytochrome P450 enzyme 5-alpha reductase or converted to estradiol by aromatase.

To maintain virility, a male needs a steady flow of testosterone in his blood stream. Without it, a person will experience abnormal growth, undeveloped male sex organs, lack of sexual characteristics, low libido, depression, decline in muscular mass and strength, and an increase in abdominal fat. Testosterone deficiency, which is not commonly encountered among young persons, may occur in their age group as a result of a medical condition that interferes with production of testosterone. It has been estimated that 0.5% of men under age 60 suffer from testosterone deficiency that is a result of a medical condition. Normally, testosterone production increases rapidly at puberty and begins to decline rapidly from the age of 40 as a result of the aging process, and continues to decrease at the rate of 0.3% a year. It has been reported that 20% of men over 60 years of age will experience a diminished testosterone production. The decrease will amount to 20 to 50% of peak level by age 80. The existence of male menopause among older persons is unclear and debatable. Treatment of this naturally occurring phenomenon in men is still controversial. Whether testosterone supplement is helpful in restoring youth is unknown. The drop in estrogen level in women is abrupt, while testosterone decline in men is subtle and gradual.

Male hormone replacement therapy (MHRT) is not routinely indicated for older individuals whose testosterone level is declining due to age. Unless there is medical need, such therapy should not be attempted. Approximately 13 million men in the U.S. complain of testosterone deficiency, and less than 10% of them undergo treatment for this disorder. Other than the aging process, testosterone deficiency can be caused by injury, infection or loss of testicles, chemotherapy or radiation treatment, genetic abnormalities, pituitary gland dysfunction, medications such as those used in the treatment of prostate cancer, chronic kidney failure, stress, alcoholism and liver cirrhosis.

Symptoms of testosterone deficiency include the following physiological changes: decrease in muscular mass (atrophy) accompanied by an increase in body fat, changes in cholesterol and lipid blood levels, bone fragility and decrease in body hair.

Testosterone deficiency can be determined by blood tests which should be conducted. Moreover, since blood levels of the hormone fluctuate during the day, several measurements need to be conducted. Most of the circulating testosterone is present in the biologically inactive form, and only 1-2% reaches tissues. Both types should be measured. Men who suffer from hypogonadism (production of insufficient amount of testosterone by the testicles) should undergo MHRT. Because men are living longer, researchers are looking into the usefulness of MHRT. A limited number of studies indicated that benefits may be gained from using this therapy.

When testosterone is used for therapy, tablets are not recommended as liver impairment may occur. The best mode of administration is the application of testosterone skin patches. These patches should be replaced with a fresh

one every 24 hours. The advantages of patches over injections are convenience and constant delivery of the drug. Injections give high blood levels of testosterone immediately, and then gradually begin to dwindle.

CONCLUSION

Menopause is a normal physiologic phenomenon that is experienced by women between the ages of 45-55 and is characterized by normal cessation of the menstrual cycle. Menopause is usually accompanied by loss in bone mass (osteoporosis) due to a decline in estrogen production by the ovaries. Hormone replacement therapy is recommended for such disorders. The risk must be weighed, however, against the benefit. Male hormone replacement therapy is not recommended as a treatment for the gradual decline in testosterone levels.

REFERENCES

- Morgentaler A, and Schulman C, "Testosterone and Prostate Safety", Front Horm Res, 37, 197 (2009)
- Stanworth RD, and Jones TH, "Testosterone for the Aging Male; Current Evidence and Recommended Practice" Clin Interv Aging., 3, 25 (2008)
- Myers JB, and Meacham RB, "Androgen Replacement Therapy in the Aging Male", Rev. Urol., 5, 216 (2003)
- M.A. Koda-Kimble, L.Y. Young, W.A. Kradjan, B.J. Guglielmo, B.K. Alldvedge, and R.L. Corelli: "Applies therapeutics", 8th ed. Lippincott Williams and Wilkins (2005)
- J.T. Dipiro, R.L. Talbert, G.R. Matzke, B.G. Wells, and L. Micheal Posey: "Pharmacotherapy", 5th Ed. McGraw-Hill (2002)

Remaining Topics for 2009

MRSA

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LESSON EVALUATION

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

Define the term "hormone," and relate their importance	Yes	No		
Describe sequence of physiological events that lead to menstruation	Yes	No		
Comment upon the role of HRT in treating osteoporosis	Yes	No		
List the adverse effects of HRT	Yes	No		
Discuss the usefulness of MHRT	Yes	No		

2. Was the program independent & non-commercial

	Yes	No		
	Average		Excellent	
	1	2	3	4
			5	6
				7

3. Relevance of topic

4. What did you like most about this lesson? _____

5. What did you like least about this lesson? _____

Please Select the Most Correct Answer

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| <ol style="list-style-type: none"> 1. Endocrine hormones: <ol style="list-style-type: none"> A. Are secreted into the bloodstream B. Are always of the peptide type C. Have potent anti-inflammatory activity D. Reach blood via a duct 2. Estrogen is released under the influence of: <ol style="list-style-type: none"> A. GnRH B. LH C. FSH D. Progesterone 3. Decline in progesterone level during menstrual cycle causes: <ol style="list-style-type: none"> A. A surge in LH level B. Thickening of the endometrium C. Fertilization of the egg D. Degeneration of corpus luteum 4. Glycogen present in the vaginal mucosa is converted by Döderlein bacilli to: <ol style="list-style-type: none"> A. Acetic acid B. Cholesterol-like chemicals C. Fatty acids D. Lactic acid 5. Which of these is not considered a major symptom of menopause? <ol style="list-style-type: none"> A. Hot flashes B. High blood pressure C. Atrophic vaginitis D. Osteoporosis | <ol style="list-style-type: none"> 6. During and after menopause: <ol style="list-style-type: none"> A. Women feel energized B. Ovaries become less responsive to FSH C. Females undergo slow bone mass loss D. Amount of progesterone increases 7. Which of these statements is correct? <ol style="list-style-type: none"> A. Cortical bones are dense & are located in the outer layer of bone B. Osteoclasts rebuild boney surfaces C. Bone mass reaches its highest level at age 45 D. Cancellous bone loss begins at age 20 8. Nocturia is: <ol style="list-style-type: none"> A. Painful urination B. Painful intercourse C. Frequent urination at night D. Inability to sleep 9. The main constituent in licorice is: <ol style="list-style-type: none"> A. Phytoestrogens B. Caffeine C. Tannins D. Glabridin 10. Which statement is correct about testosterone? <ol style="list-style-type: none"> A. Secreted only by Leidig cells B. Secreted by testes & ovaries C. Production begins to fall at age 65 D. Deficiency is less common among obese individuals |
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