



A PHARMACY CONTINUING EDUCATION PROGRAM

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

October 2008 "Pharmacy Considerations Regarding Menopause" 707-000-08-010-H05-P



*This Month: Pharmacy  
Considerations:  
Menopause*

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Surveys and focus groups from participants have placed this topic near the top of the list of those of interest. In this lesson we discuss: pharmacy considerations regarding menopause. 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 707-000-08-010-H01-P. Pharmacists completing this lesson by October 31, 2011 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. Provide an overview of menopause.
2. Discuss the conditions that may affect the timing of menopause.
3. List the symptoms associated with menopause.
4. Describe the complications associated with menopause.
5. Discuss treatment options.

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## OVERVIEW

Menopause is the time in a female's life when shutting down of the reproductive system takes place. This physiological phenomenon results in natural permanent cessation of ovulation, and the end of menstrual cycles. Clinically, menopause is often defined as the absence of menstruation for 12 consecutive months. At this time, the individual is considered to be one year into menopause. The ovaries become nonfunctional. The process does not typically occur suddenly. Usually it is gradual.

During the transition (or perimenopause time), the menstrual cycles may become erratic, short in duration, further apart, and finally cease to exist. That signals the beginning of menopause. In the course of perimenopause, it is not uncommon to experience a cycle after having none for several months. The length of time it takes for the completion of transition varies. Regardless, those who experience irregular cycles should seek medical advice to exclude other medical conditions.

The average age at onset of menopause is 51 years. This age has remained constant in spite of the fact that longevity in females has increased to 79.7 years and age of puberty has decreased. It may, however, occur as early as the 30's or as late as the 60's. Normal age range of commencement is between 45 and 55.

There are no reliable tests that can indicate in advance when menopause will start. Even though the level of Follicle Stimulating Hormone (FSH) increases and estrogen decreases, fluctuations of hormone levels cannot be used as a means of predicting that a patient is passing through menopausal transition. Premature menopause is rare. If it happens, it is anywhere from puberty to age 40. It is usually caused by premature ovarian failure, and not from the effect of aging.

Perimenopause (also known as climacteric changes) occurs as a result of diminished levels of reproductive hormones including estrogens, progesterone, and testosterone. Secretion of these hormones becomes irregular and results in diminished fertility. Reproduction is terminated when menopause is reached. It is estimated that reproductive females have approximately 400,000 ovarian follicles in both ovaries. Only about 1,000 follicles are released from the ovaries during the reproductive years. Postmenopausal ovaries are about one-third the weight of those before commencement of menopause.

In order for the follicles to mature, FSH must be present in high concentrations. However, due to an increase in age, FSH level begins to decline and follicular maturation does not occur. In the absence of maturation, estradiol-17  $\beta$  production, ovulation, and progesterone secretion do not take place. It has been estimated that premenstrual concentration of estradiol is about 120 ng/L, compared to 18 ng/L after menopause. Such decline in estradiol level may lead to prolonging the menstrual intervals, absence of ovulation, and absence of uterine bleeding. These symptoms are signs of the approaching menopause.

After menopause, the main estrogen found in circulation is estrone, which is less potent than estradiol. Prior to menopause, the daily production of estrone and estradiol are 80-300  $\mu$ g and 80-500  $\mu$ g respectively. This compares to 40  $\mu$ g of estrone and 6  $\mu$ g 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 perimenopause is progesterone. During this time, progesterone levels begin to diminish and eventually become immeasurable after menopause.

There are a number of conditions that may affect the timing of menopause:

**1. Ovariectomy** (surgical removal of one or both ovaries): Surgical removal of the ovaries results in immediate menopause because normal hormone production is abruptly terminated. There is no perimenopause, and the patient will experience the signs and symptoms of full fledged menopause.

**2. Hysterectomy** (removal of uterus): Frequently, the ovaries are removed surgically along with the uterus. However, if hysterectomy is performed without the removal of the ovaries in a fertile patient (before reaching menopause), the ovaries will continue to produce reproductive hormones without experiencing menstruation. The ovaries will remain active until normal time when natural menopause takes place.

**3. Cancer chemotherapy and radiotherapy:** Treatment of cancer with chemotherapy as well as radiotherapy in an ovulating female may result in menopause, depending on type, location of cancer and the frequency and magnitude of

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treatment. Menopause symptoms may appear during therapy or may develop within a few months following the onset of therapy.

**4. Premature Ovarian Failure:** Premature ovarian failure is a condition that may occur before the age of 40. It results in the emergence of early menopause symptoms due to lack of ovarian hormones. The cause is unknown, but it may be due to autoimmune disease or inherited genetic factors. Often no cause can be found.

**5. Miscellaneous disorders:** In many cases diseases such as diabetes mellitus, thyroid disease and autoimmune disorders may act as contributing factors.

#### MENSTRUATION

This natural process involves the shedding of the uterine lining. Typically it occurs monthly during the reproductive years. Usual cycles last from 3 to 5 days, but 2 to 7 days may be considered as normal. The average blood loss is about 35 ml. The fluid is usually a mixture of blood and endometrial lining. The presence of the enzyme plasmin tends to prevent this blood from clotting. Menstruation is the most apparent phase of the reproductive cycle, and it prepares the body for pregnancy each month. It is counted from day one of the beginning of the flow of discharge, lasts from 21 to 35 days, and the average is 28 days. Ovulation (time when egg leaves the ovary) usually occurs on day 13 or 14.

Out of all of the follicles in the ovaries, usually only one egg is released to the fallopian tube each month. In the days prior to ovulation the uterine epithelium becomes thick and vascular. This thickening of the uterine lining is necessary to provide support for the existence of the fertilized egg.

Menstruation occurs as a result of a complex interplay between the endocrine system and the target organs. The gonadotropin-releasing hormone secreted by the hypothalamus regulates the release of both luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior portion of the pituitary gland. Both LH and FSH play an essential role in stimulating the secretion of hormones by the ovaries, and in maturation of the eggs within the follicles.

Menstruation begins at puberty and ceases to exist at menopause. The sequence of events that initiates menstruation begins on the first day of the cycle. At that time, the level of estrogen in the circulation is very low. However, a gradual increase in estrogen production takes place beginning on that day. Such an increase is accompanied by an increase in the endometrial proliferation. The gradual increase in the thickness of the endometrium begins at the end of the menstrual flow and reaches maximum thickness on day 14 of the cycle. This procedure prepares the uterus for the embedding of the fertilized egg.

As stated earlier, the level of estrogen on Day 1 is low. This low level of estrogen, via the negative feedback, triggers the anterior portion of the pituitary gland to secrete FSH and LH. The FSH stimulates the ovaries to release estrogen, mainly estradiol, which eventually causes the maturation of the egg in the ovarian follicle by day 14. About 16 to 32 hours prior to ovulation, a surge of LH occurs. Under the influence of LH, one of the mature ovarian follicles rupture and an egg is released into the fallopian tube, while the other mature follicles undergo degeneration. Ovulation is usually accompanied by an increase in vaginal secretions and body temperature as well. The gradual increase in the level of estrogen, especially estradiol, which begins on the first few days of the cycle, peaks at the time of the LH surge. The level of progesterin begins to increase prior to LH surge. Thus on day 14 of the cycle, which is ovulation day, the level of LH and FSH reach their maximum. In the absence of pregnancy, this high level of LH and FSH will trigger the negative feedback of the hypothalamus-pituitary centers to stop producing LH and FSH. In the absence of FSH, stimulation of the ovaries to produce estrogen becomes negligible. A decline in the level of estrogen takes place immediately following ovulation. By day 28, the level of estrogen is so low that it leaves the endometrium without hormonal support, and the lining begins to breakdown. The blood vessels become constricted, depriving the endometrium of blood supplies. As a result, the endometrium begins to shed and a bloody menstrual discharge begins to flow signaling day one of a new menstrual cycle. The amount of discharge varies from month to month, but the average is about 30 to 40 ml. Menstruation ceases during pregnancy, during lactation and permanently at menopause.

#### SYMPTOMS

It is important to remember that menopause is a natural change in reproductive functioning and not a disease state or disorder. Therefore, the severity of the symptoms of perimenopause and menopause vary from one patient to another. Some experience few or no symptoms, while others suffer from physical and psychological symptoms such as vasomotor instability, urogenital atrophy, skeletal and muscular pain, and dermatological and psychological disturbances.

**Vasomotor instability:** An example of vasomotor instability is "hot flashes." These are experienced by 50 to 85% of patients during perimenopause and menopause. It is considered the most troublesome symptom associated with approaching menopause. It is characterized by a feeling of warmth that spreads over the body and is more pronounced in the chest, neck, and facial area. It is often associated with flushing. The patient complains of increased sweating especial-

ly at night. Hot flashing may emerge prior to the last menstrual cycle, but occurs most frequently during the two years after the beginning of menopause. They gradually diminish over time. The vast majority of patients experience these sensations for longer than 5 years. The symptoms usually last from 30 seconds to several minutes. Other vasomotor symptoms include headache, dizziness, palpitation, nausea, vomiting, night sweats, irritability, and insomnia which may lead to fatigue.

**Genitourinary Atrophy:** As estrogen begins to decline, individuals may experience symptoms associated with atrophy of the genitourinary tract. These changes may occur in the vulva, vagina, uterus, urethra and urinary bladder. The vagina becomes smaller, dry, thin, loses its appearance and becomes pale. The labia minora diminish in size, while the labia majora become less elastic, due to loss of subcutaneous fatty tissue. About 10% to 40% of patients exhibit these symptoms.

The pH of the normal healthy vagina is acidic and ranges from 4.5 to 5.0. This acidic environment provides protection against infections. During menopause, the pH reaches 6 to 8, and predisposes patients to fungal or bacterial infections.

Atrophic changes (dryness, loss of elasticity, and thinning) may also take place in both the urethra and urinary bladder. This may lead to nonbacterial urethritis, which is characterized by dysuria (painful urination), frequent and urgent urination and nocturia (frequent urination at night). Incontinence may be occasionally encountered.

**Psychological and cognitive symptoms:** During perimenopause and menopause many women report cognitive and psychological symptoms, including fatigue, memory loss, depression, anxiety, irritability, fatigue and mood disturbances.

**Dermatological changes:** Changes in skin texture like wrinkles, thinning, decreased elasticity and feeling like ants crawling on or inside the skin may be experienced by patients.

**Other symptoms:** Decreased libido, weight gain and deposition of fat in the waist and abdominal area may occur. Some patients may develop hair on the chin, upper lip, chest, and abdomen due to the continued secretion of testosterone.

#### COMPLICATIONS OF MENOPAUSE

A number of problem conditions sometimes arise.

**1. Cardiovascular disease:** Studies have shown risks associated with heart disease and strokes increase in patients in perimenopause and menopause. In fact, it has been reported that coronary heart disease rates in menopausal women are two to three times higher than those of the same age who have not experienced menopause. This increased risk is believed to be due to the decline in estrogen levels.

**2. Osteoporosis** is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue. It leads to bone fragility and increased risk of fractures. Bones are either **cortical** or **cancellous**. Cortical bones are dense and are located in the outer layers of the skeleton. Cancellous bones are situated in the interior portion. The long bones consist primarily of cortical bones, except for their ends, which are mainly cancellous. A continuous remodeling of bone occurs as a result of a balance between osteoblasts, which help in rebuilding of bony surfaces, and osteoclasts, which resorb bone. Bone mass reaches its highest level at age 30 to 35. Thereafter, cortical bone tissue begins to decline by up to 0.5% every year. At menopause, this decline accelerates and reaches 2% - 3% yearly. The reason for the reduction is believed to be diminished concentration of estradiol.

Cancellous bone loss begins during the third decade of life. At that age, the annual decrease is about 0.6 - 0.8%.

Osteoporosis is a major public health problem. It affects over 11 million people in the U.S. Obviously, its incidence increases as the patient ages. Frequency of fractures also increases with age. Over 1.5 million osteoporosis-related fractures occur yearly. Most are in the vertebrae, distal radius or hips. It has been estimated that 40% of Caucasian females over 50 years of age will suffer one of these fractures. Women who experience hip fracture have a 12% - 20% higher mortality rate. Annual costs in the U.S. that are related to osteoporosis fractures exceed \$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 an adequate quantity of vitamin D, which assists in calcium regulation, is recommended. Daily requirements range from 200-600 IU. It is also important to ensure that the patient receives about 1000 mg of calcium per day.

ERT as well as the use of bisphosphonate are recommended to prevent postmenopausal osteoporosis.

**3. Urinary Incontinence:** Loss of elasticity in the tissues of both the vagina and urethra may lead to frequent, sudden, strong urge of urination, and involuntary leakage or loss of urine.

#### TREATMENT

Risk versus benefit of estrogen replacement therapy (ERT) must be evaluated for each patient due to the possible threat of various cancers.

**Estrogen Replacement Therapy (ERT):** This is an effective way of treating the symptoms related to hot flashes. Quality of life as well as mortality caused by estrogen and progestin deficiency may improve following utilization of ERT. Such therapy may prevent osteoporosis, genitourinary atrophy and vasomotor symptoms.

Another objective is to prevent or reduce the risk of emergence of disorders associated with menopause. The rationale behind the use of ERT is to reestablish an adequate level of estrogen, thereby relieving perimenopause and menopause symptoms. The medications contained in these products usually include conjugated estrogen, estrogen substitute (i.e., diethylstilbestrol), synthetic estrogens (i.e., ethinyl estradiol) and micronized estradiol. The most widely used example is conjugated estrogen. It consists of estrone sulfate and multiple other equine estrogens. In addition to providing relief from symptoms, there is evidence to indicate that ERT can slow osteoporosis and exert positive effect on calcium balance and bone density. It has been shown that women given ERT have experienced lesser incidence of bone fracture.

Dosing information must be thoroughly explained to the patient. For long-term therapy, ERT should be administered at the lowest effective dose. The patient must be evaluated every year to determine the need for continuation of therapy. Prolonged ERT, along with the concurrent use of progestin for at least 10 to 14 days of each cycle, may be attempted in post menopausal 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 in combination of estrogen and progestin for the remainder of the month. Other regimens involve the continuous administration of estrogens along with low dose continuous 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.

A potential adverse effect of ERT, which has made it fall on negative times, is the increased risk of 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.

Additionally, the association of breast cancer with ERT 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 were not as conclusive. It does appear, however, that ERT may be falling on times of decreased use due to the potential risks. Other conditions that have been speculated about as being associated with ERT are increase in severity of incidence of thrombotic disease, hypertension, atherosclerosis, myocardial infarction, and stroke.

**Methods of Administration:** In spite of the risks, ERT is an effective therapy. If utilized, dosing should be the smallest that is effective. Short duration of action options may be the best alternative.

Estrogen occurs naturally or may be synthetically prepared. The oral route has been utilized for over 55 years.

A wide range of delivery systems are used. Estrogen may be administered orally, transdermally, intramuscularly or subcutaneously as implanted pellets. The most convenient routes are oral and transdermal.

**Oral route:** These dosage forms provide adequate blood levels of estrogen and effective relief of symptoms. It is convenient, easy to stop, relatively inexpensive, and there is a short half-life. The main disadvantage is that only 10% of the dose reaches systemic circulation due to the fact that it undergoes conversion to inactive metabolites in the GI tract. It also experiences 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 (5 mcg) and norethindrone (1 mg) in each tablet may be taken.

In case of a missed dose, the medication should be administered as soon as possible, unless it is almost time for the next dose. Instead, the missed dose should be skipped and the regular dosing schedule resumed.

**Transdermal routes:** Transdermal dosing alternatives are available as patches and gels. Transdermal estrogen is absorbed directly from the skin, and enters the circulation in a regular continuous manner. Advantages of this route are:

1. Estrogen avoids 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. Matrix patches appear to cause less adverse skin reactions than the reservoir patches. This option increases patient compliance.

One type of skin patch contains 0.025 to 0.1 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. During 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 0.1 mg of estradiol. This patch is applied to the skin and worn for 3½ days of week 1. Then it is removed, and a new one is applied and worn for the rest of the week. The patches are applied twice a week for three weeks, thereafter. 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 on the proper day, then it should be applied as soon as possible, provided that it is not time for the next patch. In that case, the missed patch should be skipped.

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.

**Crystalloid implants:** Estradiol implants (pellets) that contain 25 to 200 mcg of the hormone are inserted subcutaneously using local anesthetics. The drugs are transported directly into the circulation, thereby avoiding first-pass hepatic metabolism. The pellets help 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 the 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 option is that minor surgery is required for insertion and removal, enhancing the risk of infection.

**Vaginal routes:** Estrogen therapy via this route of administration is usually intended to achieve local effects rather than systemic. Menopause can result in atrophic vaginitis and vulvular atrophy. Local estrogen therapy is sometimes effective in minimizing these symptoms. Vaginal preparations include creams, inserts (rings) and suppositories.

Creams are applied with an applicator. For treating vulvular atrophy and atrophic vaginitis in post menopausal patients, one half to two grams of conjugated estrogen cream containing 0.3 to 1.25 mg is inserted 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 gm of cream) once a day for one to two weeks, decreasing the dose by one-half for weeks two to four. After four weeks, the dose and its frequency maybe reduced.

The drawbacks of vaginal creams are the difficulty of measuring and administering the cream for older 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 a biologically inert liquid polymer matrix that is 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.

Estrogen vaginal suppositories each contains 250 to 500 mcg, and are usually administered once daily or as directed by the physician.

#### ALTERNATIVE (NATURAL) MEDICINES

A number of complementary and alternative treatments are sometimes used.

**1. Phytoestrogens:** These are derived from plants. They structurally and functionally resemble estrogen synthesized by the body. These chemicals are widely found in oil seeds, vegetables and soy beans. There are two main types of phytoestrogens: a) isoflavones and b) lignans.

There are a number of herbal products that have been utilized for menopausal symptoms. However, recent research to determine the active ingredients, mechanism of action and potential clinical usefulness gave varying degrees of benefit of phytoestrogens for symptomatic relief of menopause. Safety studies for herbal products during pregnancy and lactation are inconclusive.

**2. Soybeans and isoflavones:** The main active constituents of soybeans and chick peas are isoflavones. They possess weak estrogenic activity ranging from 500 to 15,000 times less than that of estradiol. Reports indicating that use of soybeans to relieve or reduce hot flashes are inconclusive.

**3. Dong quai** has been used for hot flashes as well as other menopausal symptoms. Even though its efficiency is questionable, its safety profile appears to be good.

**4. Black cohosh** is an herb native to eastern North America. Native Americans used black cohosh for treating amenorrhea and menopause. Black cohosh is sometimes used as a natural alternative for the treatment of hot flashes, menopausal anxiety and depression. Extracts from the drug have been used in younger women suffering from hormonal

deficiency following ovariectomy or hysterectomy, as well as juvenile menstrual disorders. However there is no evidence to prove its effectiveness in treating menopause symptoms.

**5. Licorice root:** Several isoflavones from licorice root have been isolated. Of these glabridin is the main constituent (11%) of an alcohol extract. Its lipophilic nature and structure are similar to natural estrogen. It has been shown that glabridin and its derivatives function as estrogen agonists. Presently there is no documentation to show potential effectiveness of licorice root as an alternative to ERT.

**6. Vitamin E:** This vitamin has been said to provide some relief from mild hot flashes in some patients. It is not clear how the benefit may be gained, or if it is truly effective.

#### SUMMARY

Menopause is a natural physiological phenomenon experienced in women around the age of 51. The treatment consists of therapy for symptomatic relief.

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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?

- |   |     |    |
|---|-----|----|
| Provide an overview of menopause                    | Yes | No |
| Discuss conditions that affect timing of menopause  | Yes | No |
| List symptoms of menopause                          | Yes | No |
| Describe complications of menopause                 | Yes | No |
| Discuss treatment options associated with menopause | Yes | No |

2. Was the program independent & non-commercial Yes No

	Poor		Average		Excellent		
3. Relevance of topic	1	2	3	4	5	6	7

4. What did you like most about this lesson? \_\_\_\_\_

5. What did you like least about this lesson? \_\_\_\_\_

**Please Select the Most Correct Answer**

- |  |  |
|--|--|
| <p>1. If premature menopause occurs, it may be due to:<br/>                 A. Ovarian failure<br/>                 B. Atherosclerosis<br/>                 C. Aging<br/>                 D. Thrombocytopenia</p> <p>2. What is the average age of onset of menopause?<br/>                 A. 45<br/>                 B. 51<br/>                 C. 60<br/>                 D. 65</p> <p>3. Maximal endometrial thickness is usually on which day of the cycle?<br/>                 A. 1<br/>                 B. 10<br/>                 C. 14<br/>                 D. 28</p> <p>4. LH &amp; FSH levels are maximal on which day of the cycle?<br/>                 A. 1<br/>                 B. 14<br/>                 C. 28<br/>                 D. None of these</p> <p>5. "Hot flashes" are an example of:<br/>                 A. Psychological symptoms<br/>                 B. Vasomotor instability<br/>                 C. Thermostatic instability<br/>                 D. All of these</p> | <p>6. The main side effect associated with transdermal estrogen patches is:<br/>                 A. Vomiting<br/>                 B. Nausea<br/>                 C. Application site irritation<br/>                 D. None of these</p> <p>7. Which form of estrogen is primarily present after menopause?<br/>                 A. Androstenedione<br/>                 B. Estradiol<br/>                 C. Estrone<br/>                 D. Progesterone</p> <p>8. Lack of menstrual cycle is defined as:<br/>                 A. Amenorrhea<br/>                 B. Premenorrhea<br/>                 C. Dysmenorrhea<br/>                 D. Pliomenorrhea</p> <p>9. ERT is administered via all of these routes, except:<br/>                 A. Transdermal<br/>                 B. Oral<br/>                 C. Implants<br/>                 D. IV</p> <p>10. Which statement is true regarding phytoestrogens?<br/>                 A. Found in soybeans<br/>                 B. Resembles testosterone<br/>                 C. Contain no isoflavones<br/>                 D. Not effective for hot flashes</p> |
|--|--|

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**Program ID #707-000-08-010-H01-P.**

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