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REVIEW ON HORMONAL CHANGES IN MENOPAUSE

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Abstract

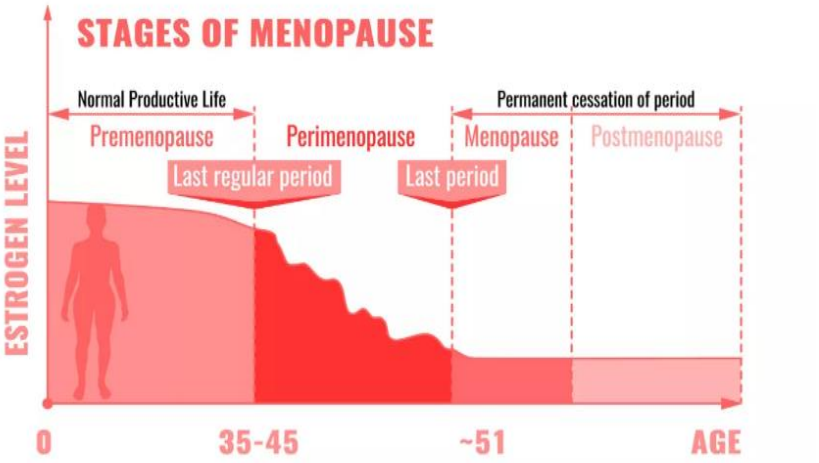
The menopause is a physiological event that occurs in all women who reach midlife symptoms shown to be associated with oestrogen deficiency after the menopause are hot flushes and night swat, insomnia and vaginal dryness.
However, many other symptoms and conditions (irregular menstrual bleeding, osteoporosis, arteriosclerosis, depressed mood, irritability, forgetfulness, dizziness, palpitation, restless legs, muscle and joint pain) have also been implicated as associated with menopause but are not oestrogen levels.
Menopause is the final stage of ovarian physiology in women, and represents the time when reproductive function is lost due to complete depletion of the finite ovarian supply. oestrogens are effective in treating vasomotor symptoms, urogenital atrophy symptoms and irregular menstrual bleeding that occurs in the perimenopausal period. Conjugated oestrogens are given orally, and estradiol may be given orally as tablets or transdermaly as a patch or gel for a period of 3 weeks or longer. Perimenopausal women and women during the first to 2 years after the menopause who have an intact uterus must be treated with a oestrogen for at least 12 to 14 days every month in order to prevent endometrial hyperplasia and possible endometrial cancer.

Keywords: Menopause, women, estrogen, hormone.

I. Introduction

The menopause is a physiological event the occurs in all women who reach midlife. Menopause is a normal change in a woman's when her period stops. That's why some people call menopause The change of life. During menopause a women's body slowly produces oestrogen and progesterone. This often happens between the age of 45 to 55 years.
There are steps in menopause:

- Premenopause
- Perimenopause
- Menopause
- Postmenopause



II. Physiology of the menstrual transition

Menopause is the final stage of ovarian physiology in women, and represents the time when reproductive function is lost due to complete depletion of the finite ovarian supply. (13)
The menopausal transition occurs by diminishing pool of ovarian follicles and is marked by fluctuation in reproductive hormones and changes in menstrual pattern. this is accompanied by menstrual irregularities and ending with Final menstrual period (FMP).
The median duration of the menopause transition is approximately 4 years. Symptoms of menopause typically start off mild and then increase in prevalence later in the transition as prolonged amenorrhea and hypooestrogenism predominate. Irregular bleeding patterns, with changes in period frequency and bleeding duration, may be one of the earliest signs of the menopause transition, and are often associated with anovulation. Symptoms are most prevalent and severe during the first 1-2 years after the FMP.(13,11)
Unfortunately, earlier symptom development in the transition portends a longer duration of bothersome symptoms, and some women will experience bothersome symptoms for more than a decade. While AMH has been shown to help predict time to natural menopause, its predictive effect lessens with increasing age. A prospective study of AMH levels predicting early menopause of women age 35-44 showed for every decrease of AMH by 0.10 ng/ml below 2 ng/ml, a 14% higher risk of early menopause before age 45. Thus, AMH levels may help guide clinicians in combination with symptom assessment to determine who is at risk for menopause and initiate appropriate treatment. (14)

III. Stages of menopausal transition

These stages are based on the menstrual bleeding patterns, and changes in hormonal levels:

1. The late reproductive stage
2. The early menopause transition
3. The late menopause transition
4. Early post menopause

1. The late reproductive stage

In this stage ovarian reserve i.e. the number of follicles remaining in the ovaries begins to decline. Along with overt changes in menstrual cycling, with hormonal changes compensating for decreasing follicle count to maintain regular ovulatory cycling.(1)
Anti-mullerian hormone (AMH), produced by granulosa cells of small, growing follicles i.e. preantral and antral follicles.
This anti-mullerian hormone reaches a peak around 25 and then declines continuously throughout reproductive life. Inhibin B, produced by larger, growing follicles i.e. antral and preovulatory follicles is also became lower at this stage and it contributing to inhibition on production of follicle stimulating hormone (FSH) by pituitary gland.(1) These changes are subtle and inconsistent from cycle to cycle to cycle. FSH may be normal or intermittently elevated at this stages, and menstrual cycle may be normal to slightly irregular.(15)

2. The early menopausal transition

A woman has entered the early menopausal transition when she experiences a > 7day difference in cycle length of consecutive menstrual cycles. The woman who enter the menopausal transition at a young age tend to have a longer duration of early and total transition. At this stage, the continued depletion of ovarian follicles and declines in AMH further release further release inhibition on follicle activation, and follicle activation and growth are maintained in the face of dwindling follicle counts.(14,15) Follicles have fewer granulosa cells, increases in follicular aromatase activity preserve estradiol levels, resulting in equal or greater oestrogen levels than mid-reproductive age women. (15)
After ovulation, diminished production of progesterone and inhibin A by the corpus luteum compared to mid-reproductive aged women is observed, likely due to reduced follicle quality. This reduced luteal phase feedback allows FSH to rise in the luteal phase and recruit the dominant follicle of the next menstrual cycle even prior to menses. This phenomenon can manifest in a shorter subsequent menstrual cycle, with short cycles being more common in the early menopausal transition. a rise in progesterone or its urinary metabolite, pregnanediol glucuronide, in the luteal phase Thus, compensatory mechanisms during the early menopausal transition (e.g. elevated FSH, increased follicular aromatase activity) are largely effective in maintaining cyclicity and fertility with some irregularity. (5)

3. The late menopausal transition

When a woman experiences an interval of amenorrhea ≥60 days, she has entered the late menopausal transition, which is more consistent in duration and lasts around 1-3 years. At this stage, compensatory mechanisms fail and more stark changes are observed- in addition to the abnormal menstrual cycles described above, in this stage FSH is more consistently elevated, oestrogen levels still fluctuate but are more consistently low, Pdg continues to decline, and cycles are less likely to demonstrate evidence of luteal activity.

An ovulatary cycles have varying underlying hormonal patterns, which have been classified as:

a) Normal rise in follicular phase oestrogen and normal surge of luteinizing hormone (LH), but lack of rise in luteal Pdg indicating ovulatory failure.
b) Normal rise in follicular phase oestrogen but failure of the LH surge, indicating hypothalamic-pituitary insensitivity to oestrogen positive feedback.
c) No rise in oestrogen and no LH surge, though LH is elevated above basal levels despite premenopausal oestrogen levels, believed to be due to hypothalamic-pituitary insensitivity to oestrogen negative feedback. There is substantial variability in these cycle types within women, such that each individual may demonstrate different anovulatory patterns as well as revert to ovulatory patterns, without clear predictability. When ovulatory cycles do occur in the late menopausal transition, the cycles are of normal length and can appear hormonally normal, indicating that windows of fertility may exist up until the FMP. (1)

4. Early post menopause

Entering the early postmenopausal stage is determined, when 12 months have passed since a woman's last menses. In this stage, ovarian reserve is very low (i.e. undetectable), and FSH continues to rise while oestrogen continues to fall, until they stabilize approximately 2 years after the FMP.

IV. Signs and symptoms

In the months or years leading up to menopause (perimenopause) might experience signs and symptoms like,

- Acne
- Anxiety
- Bloating
- Breast tenderness
- Crying
- Decreased libido
- Facial hair
- Forgetfulness
- Frequent need to urinate
- Hair loss or thinning
- Headaches
- Hot flashes
- Interrupted sleep
- Irregular periods
- Mood swings
- Night sweats
- Urinary incontinence
- Vaginal dryness
- Weight gain, especially around the mid life

Sleep problems during menopausal transition

Sleep difficulties increase in prevalence as women transition menopause. For some women, sleep problems are severe and impact daytime functioning and quality of life and may have long-term consequences for mental and physical health. There are various factors that contribute to the development of sleep disturbance in the context of the menopausal transition. HFs are a unique aspect of insomnia in the menopausal transition and are strongly associated with reports of disrupted sleep, and HF-associated wakefulness makes a significant contribution to the amount of PSG-measured wakefulness during the night. In addition, given the co-occurrence of HFs and awakenings, women attribute those awakenings as specifically caused by HFs. Since some women may have sleep problems independent of HFs, other factors directly related to the menopausal transition (e.g, instability/changes in the hormone environment with progressive decreases in estradiol and increases in FSH) and/or coincident with the transition (eg, SDB or movement disorders, mood disturbance, presence of a medical condition, and life stressors) also need to be considered. (27) It, therefore, is critical to assess insomnia symptoms in the context of menopause as well as considering physical and mental health and presence of stressful life events. Given the presence of unique sleep-disruptive factors (eg, HFs) and the multifactorial nature of sleep difficulties in women approaching menopause, with multiple factors often interacting, treatment needs to be tailored for women. (4, 12)

Mood

Mood changes marked by increased depression and anxiety are common during the menopause transition. Depressive symptoms peaked in the late perimenopause. While women with a history of depression are at risk for future depression, women without a pre-existing history are at risk during menopause, with a 16% prevalence of new-onset depression and/or anxiety. Longitudinal studies suggest a longer menopause transition is associated with depression, probably due to increased symptoms. Other risk factors for depression as women approach the menopause transition include nulliparity, separation from a prior spouse, premenstrual symptoms and smoking. Hormone changes and neuro steroids are believed to contribute to dysregulation of the gamma amino butyric acid (GABA) balance between GABA-A and GABA-B to increase vulnerability to depression during this time of life. Adverse early life events may also play a role in predisposing women to adverse mood in midlife. Interestingly, HT may improve mood in the absence of significantly reducing VMS in perimenopausal women. Although VMS associate with new onset of depressive mood, a reciprocal relationship between VMS and new onset of major depression is not as clearly demonstrate. (1,16)

Cognition

Cognitive decline is mostly associated with somatic aging rather than menopause. Several studies have refuted the benefits of ooestrogen on cognitive function. cognitive functioning declines during the menopause transition, but appears to return to baseline by the transition's end. This study suggested a limited decline, however, a secondary analysis of the cohort for 6.5 years found age-related processing by Rice University user on 23 October 2020 Accepted Manuscript 12 speed and memory decline, suggesting within-woman age-related cognitive decline persisting beyond the menopausal transition. When ooestrogen hormone therapy was initiated in perimenopausal women it protected cognitive performance, but when initiated in postmenopausal women it veered on harm. The Cognitive Affective Study of the Kronos Early ooestrogen Prevention Study (KEEPS-Cog) treated early postmenopausal women with 4 years of HT but found no appreciable difference in cognition compared to placebo suggesting HT neither harms nor improves cognition in early postmenopausal women. (16,17,22)

Libido

Decreased sexual desire is prevalent during the menopause transition and may affect as much as 10% of women. The Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study showed increased problems with sexual desire in women 45-64 years compared to both older and younger females. Less than half of these women have concurrent depression. The hypooestrogenism and decline in testosterone levels associated with aging contribute to these symptoms. Testosterone replacement in women with and without ovaries has been performed and shown modest benefit on sexual desire and satisfaction per sexual episode. Importantly, large studies evaluating both the efficacy and safety of testosterone replacement, particularly risk of breast cancer, in menopausal women are lacking. There are two pharmaceutical agents approved for treating hypoactive sexual desire disorder in pre-menopausal women, bremelanotide and flibanserin. Bremelanotide is a melanocortin receptor agonist that activates several receptor types, most notably MC1R and MC4R in the CNS. Flibanserin is a 5-HT1A receptor agonist and 5 Flibanserin is a 5-HT1A receptor agonist and 5- HT2A receptor antagonist. There are currently no FDA-approved formulations for post-menopausal women with low libido. (23, 24)

Bone

Oestrogen is a potent anti-resorptive agent at the level of the bone, and thus hypooestrogenism of menopause marks a period of increased rate of bone resorption. Osteoporotic fractures affect half of women after age 50. Oestrogen promotes osteoblasts and increases calcium absorption from the intestines. Loss of oestrogen decreases calcium absorption which promotes osteoclast-mediated bone resorption via upregulated parathyroid hormone. Peak anabolic bone mineral density is achieved around age 30 and progressively declines thereafter at approximately 0.7% per year. Rates of bone loss increase dramatically starting a year before the FMP, and persist up to 3 years with rates of bone loss as high as 5% per year, then slows again to approach the rate of loss prior to menopause. (9)

Hot flashes

A hot flash is a sudden feeling of heat in the upper body.It may start in the face, neck or chest, and then spreads upwards or downwards. The heart rate may suddenly increase or may become irregular or stronger than usual palpitations. Hot flashes occur during the first year after a woman's final period. Hot flashes result from the body's reaction to a decreased supply of the hormone oestrogen, which occurs naturally as women approach menopause. For some women, oestrogen production decreases gradually, producing fewer hot flashes. (16,20)

Night sweats

Night sweats occurs during sleep in menopausal women. For many women, the experience of night sweats is on sever, that it disrupts sleep and it may increase irritability and stress in a women's waking life. (16)

Irregular periods

Menstrual pattern will start to change some women may experience a period every two to three weeks, while others may not have one for months at a time Irregular period occurs in decreasing levels of oestrogen and progesterone. (21)

Vaginal dryness

Vaginal dryness occurs when the usually moist and soft feeling of the lining of the vagina disappears, bringing about symptoms such as itchiness and irritation. when oestrogen levels drop during perimenopause, the vaginal tissue becomes drier, thinner, and less elastic. Lack of lubrication leads to sex becoming uncomfortable, and the vagina is frequently itchy, easily irritated, and more prone to infections. These may include brittle nails, thinning of the skin, hair loss and generalized aches and pain. these are due to falling oestrogen levels. (24,26)

V. Hormonal Effects of menopause

Changes in androstenedione, dehydroepiandrosterone, testosterone, estradiol, and estrone over the menopausal transition

The menopausal transition (MT) represents a marked shift in women's sex steroid profile, of which changes in estradiol (E2) are the best studied. On average, women's estradiol concentrations begin to change more rapidly about 2 years prior to the final menstrual period (FMP) and stabilize several years after the FMP. The rapidity of decline and average estradiol levels may be predicted by race/ethnicity and body mass index (BMI) at the beginning of the transition. As adrenal sex hormones exist in equilibrium with ovarian sex hormones in the peripheral circulation, it is plausible that adrenal hormone metabolism also changes over the MT. This is consistent with the hypothesis that increasing adrenal sex hormone production and aromatization may be concurrent with decreasing ovarian oestrogen production. It is also possible that DHEAS production may also eventually decline over time resulting lower peripheral A4 and E1 concentrations. changes in a comprehensive array of adrenal sex hormones across the MT. Since concentrations of circulating DHEAS increase in the 5th decade of life. (5,7)

Follicle-stimulating hormone

Follicle-stimulating hormone (FSH) is known as pre-requisites for follicular maturation and regulator of ovarian oestrogen synthesis in women. However, the role of FSH in glucose metabolism has not been studied. In female dog, FSH plus luteinizing hormone (LH) treatment increases the serum insulin response to glucose load. Increased LH/ FSH ratio is a common characteristic of women with polycystic ovary syndrome (PCOS), which is reported to be associated with insulin resistance and obesity in PCOS. (1,2) A most recent study also found that lower FSH was significantly associated with high prevalence of metabolic syndrome in postmenopausal women, but the sample was relatively small. Though there are no population-based data on the association between FSH and DM in general people, FSH is found to be associated with adiposity in women, which is also a great risk factor for type 2 DM. (3)

	Estrogen	Progesterone	Testosterone
What does this hormone does?	Stimulates growth of breast. Maintains vaginal blood flow.	Prepares lining of the uterus for s fertilized egg and helps maintain early pregnancy.	Contribute to libido. May help maintain bone and muscle mass.
Effect by menopause and age	During perimenopause, level fluctuate and become unpredictable.	Production stops during menstrual cycles when there is no ovulation and after final menstrual period.	Ovaries continue to make testosterone even after oestrogen production stops. Testosterone production from adrenal glands with aging but continues after menopause.
Symptoms	High levels can result in bloating breast tenderness, heavy bleeding.	Lack of progesterone can cause periods to become irregular, heavier, and longer during menopause.	Effects of testosterone decline are uncertain.

VI. Diagnosis

There is no one test to diagnose menopause Symptoms may indicate that menopause is imminent but menopause can only be confirmed retrospectively after periods have been absent for one year. Blood tests may be taken at this time as the levels of hormones produced by the pituitary gland - follicle stimulating hormone (FSH) and luteinizing hormone (LH) be higher if menopause has occurred. A change in bleeding patterns, particularly where periods become heavier, and an absence of periods (amenorrhoea) can indicate various medical condition. It is therefore advisable to consult a doctor before assuming that the changes are menopausal symptoms. Also, if bleeding occurs after periods have been absent for a year, a doctor should be consulted, as this is not considered normal. (11, 18)

VII. Possible complications

Oestrogen is responsible for the buildup of the lining of the uterine city During the reproductive years, this buildup occurs and then is shod Concentration. This usually happens about a once a month. The menopausal decrease in oestrogen prevents this bust day from surring However, hormone produced by the adrenal glands are converted to oestrogen, amil sometimes this will cause postmenopausal blooding. This is often nothing to worry about, but because postmenopausal bleeding may also be an indication of other problems, including cancer, a physician should always check any postmenopausal bleeding Decreased oestrogen levels are also associated with an increased risk of developing osteoporosis and possibly an increased risk of cardiovascular disease. (25, 10)

VIII. Prevention

Menopause is a natural and expected part of a woman's development and does need to be prevented. However, there are ways to reduce or eliminate some of the symptoms that accompany menopause.

- You can also reduce your risk of long-teres problems like osteoporosis and heart disease
- DO NOT smoke cigarette use can cause early mesopause
- Exercise regularly to strengthen your bones, including activity that works with the resistance of gravity.
- Take calcium and vitamin D.
- Eat a low-fat diet.
- If you show early signs of bone loss, talk to your doctor about medications that can help stop further weakening Control your blood pressure, cholesterol, and other risky factors for heart disease.

IX. Menopause-medicines to help you

woman choose to treat their menopause symptoms with hormone medicines times called Hormone Therapy.
Do not take hormone therapy if you;

- Have problems with vaginal bleeding.
- Have or have Certain cancers such as breast cancers such as breast cancer or uterine cancer.
- Have a blood clot, stroke or heart attack.
- Have a bleeding disorder.
- Have liver disease.
- Have allergic reactions to hormone medicine.

X. Side Effects

Hormone medicines have side effects. For some women, hormone medicines may raise their chances of blood clots, heart Backes, strokes and breast cancer.

XI. Menopause Hormone Therapy

There are different kinds of hormone medicines used during and after menopause:

- Oestrogen-only medicines
- Progestin-only medicines (These medicines are taken along with Oestrogen Medicines.
- Combination Oestrogen and Progestin Medicines.
- Combination Oestrogen and Hormone Medicines.

Oestrogen-only medicines

Brand name	**Generic name**	**Product Type**
Alora	Estradiol	Patch
Cenestin	Synthetic	Pill
Divigel	Estradiol	Gel
Elestrin	Estradiol	Gel
Estraderm	Estradiol	Patch
Estrasorb	Estradiol	Skin cream
Femtrace	Estradiol Acetate	Pill
Premarin	Conjugated Estradiol	Pill, vaginal cream, Injection
Minivelle	Estradiol	Patch

Progestin-only medicines

Brand Name	**Generic name**	**Product type**
Prometrium	Micronized progesterone	Pill

Combination Oestrogen and Progestin Medicines

Brand Name	**Generic name**	**Product type**
Activella	Estradiol/ Norethindrone Acetate	Pill
Angeliq	Estradiol/ Drospirenone	Pill
Climara pro	Estradiol Levonorgestrel	Patch
Combipatch	Estradiol/ NorethindroneAcetate	Patch
Femhrt	Norethindrone Acetate/ Ethinyl Estradiol	Pill
Prefest	Estradiol Norgestimate	Pill
Prempro	Conjugattitted Esterogen/ Medroxyprogesterone	Pill

Combination Oestrogen and Hormone Medicines.

Brand Name	Generic name	Product type
Duavee	Conjugated Esterogen/ Bazedoxifene	Pill

XII. Diseases related to menopause

Rheumatic autoimmune diseases in women's midlife

Autoimmune diseases are characterized by systemic inflammation, in which a dysregulated immune system causes damage or dysfunction to target organs. Rheumatic autoimmune diseases include conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (scleroderma), in which the connective tissues (cartilage, joint synovium, skin) are most frequently targeted. (9)

Autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis (scleroderma) preferentially affect women, and are characterized by systemic inflammation leading to target organ dysfunction. The public health burden of autoimmune diseases, which collectively represent a leading cause of morbidity and mortality among women throughout adulthood, is substantial. While some features of these diseases have been observed to improve over the menopausal transition, such as disease flare rate in SLE and skin softening and thinning in scleroderma, others, such as swollen and tender joints and radiographically confirmed damage in RA may worsen. The general trends, however, are not consistent or conclusive for all disease-related manifestations. Of great importance is the recognition that comorbid diseases, including osteoporosis and accelerated cardiovascular disease, contribute excess morbidity and mortality that becomes increasingly apparent as women with autoimmune diseases undergo the menopausal transition. rheumatic autoimmune diseases can occur across the lifespan, the typical presentation occurs in mid or late- adulthood. These diseases are considerably more common in women than in men, with approximately 90 % of prevalent cases being female for SLE and scleroderma, and approximately 75 % for RA. (9,20)

Chronic Vulvar pain

postmenopausal vulvar pain is frequently attributed to vaginal atrophy, such symptoms may be due to vulvodynia, a chronic vulvar pain condition. Given the limited research on vulvodynia in postmenopausal women, the objective of this study was to provide preliminary population-based data on the associations of vaginal symptoms, serum hormone levels and hormone use with chronic vulvar pain in a multiethnic sample of post-menopausal women. Some women who experience chronic vulvar pain symptoms do not report vaginal dryness, and others report continued or first onset of pain while using hormones. Vulvodynia should be considered in the differential diagnosis of postmenopausal women presenting with vulvar pain symptoms. (24)

Although vulvar pain symptoms can occur at any time over the life span, it is not uncommon for symptoms to begin for the first time after menopause. In fact, the prevalence of chronic vulvar pain in mid-life women has been estimated to be 8.9-38 % percent, making chronic vulvar pain a major health concern for women in this age group. (26)

Osteoporosis

Osteoporosis is a bone disease that develops when bone mineral density and bone mass decreases, or when the quality or structure of bone changes. (9) This can lead to a decrease in bone strength that can increase the risk of fractures (broken bones). Osteoporosis is the thinning of bones that can lead to fractures; unfortunately there are no warning symptoms of this disease However other common symptoms are mood changes (including irritability and anxiety), muscle and joint pain, changes in hair and skin quality, sleep disruption, headaches and digestive disturbances. When women get to perimenopause oestrogen production from the ovaries slows and finally stops at menopause. However the adrenal glands should continue to produce oestrogen at around 40% of previously combined levels – and this should be sufficient to continue to maintain bone mass and as such bone health. (11,15)

XIII. Conclusion

Menopause is a physiologic event. Today, several options exist for the treatment of the endocrinological changes associated with the menopause estrogen deficiency can be corrected with hormone replacement therapy and topical preparations Estrogen with or without testosterone may improve general well-being in some groups of surgically menopausal women. Levels of serum estrogen achieved in this studies were within a normal range for premenopausal women. Adding testosterone to estrogen therapy may provide additional improvements is well-being in some women, but only at super physiological levels of total testosterone and physiological levels of free testosterone.

XIV. Summary

The medical definition of the menopause is the end menstruation which reaches from a reduced production of estrogen by the body Menopause, as part of a women's ang process 91 percent of peri-and postmenopausal women have sought treatment for menopause symptoms at this stage of their lives. The menopause is a time of normal physiological change in a women's life that often coincides with changing family or work environment. The transition through the menopause varies greatly among women both within and across cultures. Hot flashes, the most common complaint of the perimenopause During the menopause a women may still have monthly blists but the number of menstrual cycles, when no egg is released from the ovaries, increases. The level of female hormones, estrogen and progesterone, may fluctuate almost daily around the time the menopause. Women's periods then stop due to the consistently low levels of estrogen. Given adequate time for reflection and reassessment women generally emerge positive, refreshed, happy and produced to have managed their menopause.

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