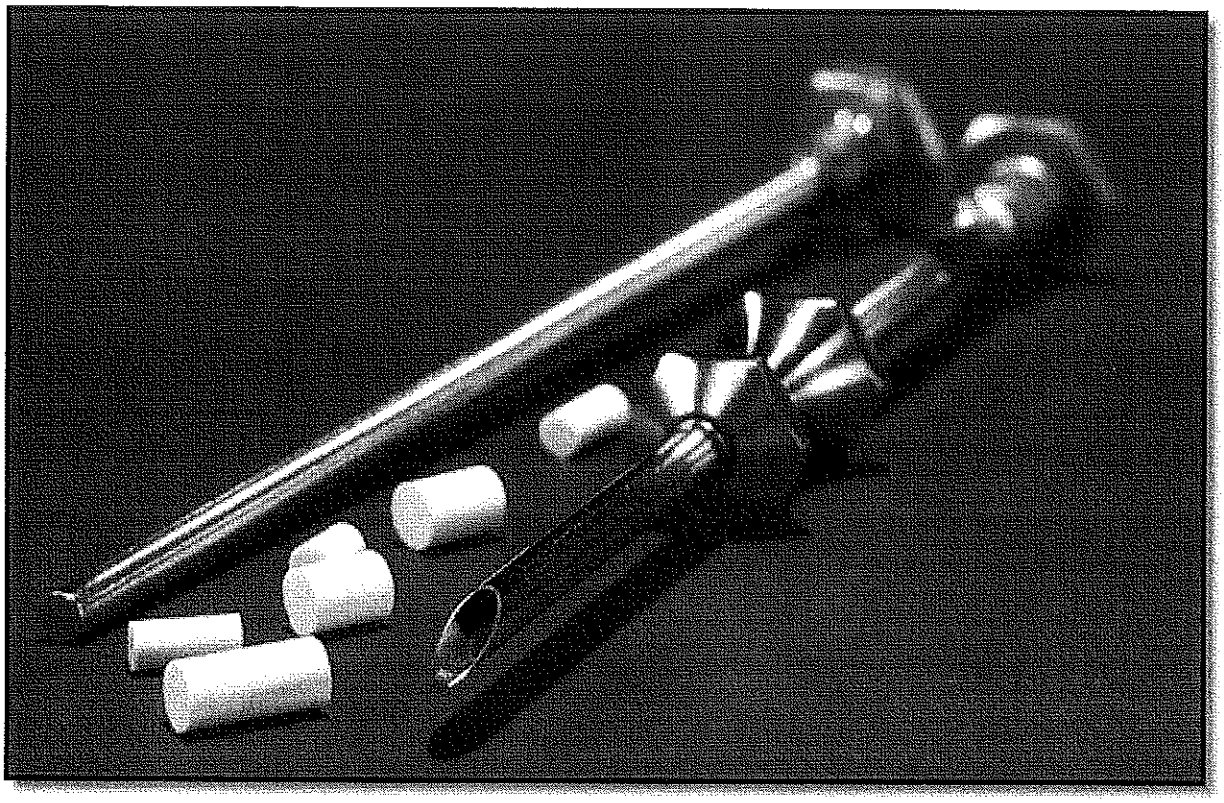
The use of Implantable Hormone Pellets in Perimenopausal and Postmenopausal Women



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Infertility Elective Rotation

I. Introduction

It is estimated that 75% of women are in an estrogen deficiency state within a few years after the onset of menopause.[5] For years, physicians have been using pharmacologic treatment and Hormone Replacement Therapy (HRT) for the menopausal symptoms. Hormone therapy should be initiated after a careful evaluation of the patient to eliminate serious disorders and adverse effects. Among the HRT, oral and injectable modalities have long earned their place in therapy.[5] For ten to fifteen percent of estrogen-deficient females, taking oral HRT is not completely satisfactory because of the unreliability in taking the drug, poor drug absorption, and untoward effects such as headache, nausea, and incomplete relief.[5] Although hormone pellets have been used since the late 1930s, many physicians are unaware that they exist.[1] These pellets are composed of testosterone or estradiol, an estrogen steroid hormone. These hormones are fused into solid cylinders which are then placed subcutaneously by the physician. Hormone Replacement Therapy by pellet implantation has been used with great success in the United States, Europe and Australia since 1938 and was found to be superior to other methods of hormone delivery.[2] It has been shown that these subcutaneous pellets deliver a consistent and balanced physiologic levels of hormones for a period of months, making them superior other forms of HRT, like the injectables and oral modalities, where a fluctuating hormonal level has been.

One of the benefits of using subcutaneous hormones is that they bypass the liver. By doing so, the clotting factors that are usually affected by these hormones are not affected, thus reducing the risk of thrombosis. Subcutaneous testosterone has been shown to be cardio protective by lowering LDL levels and raising HDL levels, unlike the oral form. It does not adversely affect the liver functions, blood pressure nor serum glucose levels. Multiple studies have been made to show the benefits of using subcutaneous hormones. Some studies have shown that these are a very effective delivery system to maintain and reverse bone loss when compared to other forms of hormone administration.[3] Subcutaneous Pellet Hormone implants have been used for a long time and offer a wide range of benefits for patients with menopause, migraines and headaches, insomnia, decreased sex drive and libido, mood imbalances, among others. We will discuss the physiology of these hormones, the indications of this therapy for patients, risks, complication and benefits, contraindications and the technique of hormone pellet placement.

II. Physiological action of estrogen, progesterone and testosterone

The women's reproductive life is regulated by the production of estrogen and progesterone by the ovaries. The sources of estrogen are the ovaries (17B-estradiol), blood (aromatization) and placenta (estriol) by the stimulation of LH and FSH on Theca cells and Granulosa cells, respectively. During puberty, estrogen functions in the development of the female sex characteristics like breasts, genitalia and female fat distribution. Other functions of estrogen are in maturation and maintenance of the uterus, up regulation of LH receptors, progesterone and estrogen itself, stimulates and blocks prolactin secretion, up-regulates HDL cholesterol and down-regulates LDL cholesterol, regulates the menstrual cycle. Progesterone is produced by the placenta, testes, adrenal cortex and corpus luteum. It functions to maintain pregnancy, prevents of uterine contraction by relaxing the uterine smooth muscle, stimulates endometrial glandular secretion, increases the basal body temperature due to an increase in the

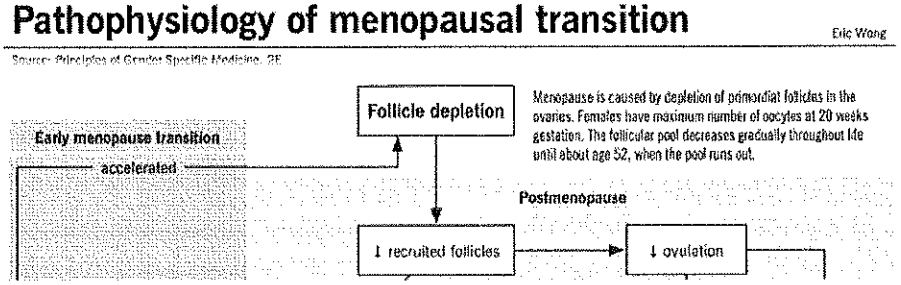
hypothalamic temperature set point, down-regulates estrogen receptors, and decreases LH and FSH levels during the luteal phase of the menstrual cycle.

Testosterone is synthesized by Leydig cells of testes via a biosynthetic pathway beginning with a cholesterol precursor. In addition to testosterone, Leydig cells of the testes also produces dihydrotestosterone (DHT), which is catalyzed from testosterone by 5a-reductase. DHT is the most potent of the androgens (DHT > Testosterone > Androstenedione). Testosterone functions in fetal differentiation of internal male genitalia during embryogenesis. It stimulates the development of the epididymis, seminal vesicles, and vas deferens. It plays an important role during puberty by aiding in deepening of voice, growth of penis and seminal vesicles, increasing sex drive and libido and increasing muscle mass. Indirectly, plays a role in cessation of pubertal growth spurt by promoting the closure of epiphyseal plate. DHT plays an important role during embryogenesis in fetal differentiation of the external male genitalia (prostate, penis and scrotum). It also promotes the male pattern baldness, male hair pattern, prostate growth and sebaceous gland activity.

III. Hormonal imbalance during menopause

Menopause is the permanent cessation of menstrual cycles resulting from loss of ovarian follicular activity usually during a women's fourth and fifth decade of life. It is caused by a depletion of primordial follicles in the ovaries (figure 1). As women ages, the follicular pool decreases until it completely runs out. This, in turn, results in a gradual decrease in inhibin B, the major regulator of FSH (follicle stimulating hormone).[4] Due to the gradual loss of inhibin B's negative feedback on FSH, there will be an increase in FSH levels and in estradiol for some years before the follicular pool is completely depleted and the estradiol levels decline. A decrease in Sex-hormone binding globulin (SHBG) will also contribute to an increase level of free, bioavailable estrogen. This is called the early menopausal transition.

The early menopausal transition starts when women experiences menstrual irregularities after previously regular cycles. This is caused by inhibin B's gradual decrease. Eventually, anovulatory cycles will occur once menstrual irregularity is established. The late stage of menopausal transition is marked by sixty to ninety days of amenorrhea and anovulatory cycles. At this stage, FSH and LH levels are elevated but Estradiol, Anti-mullerian hormone (AMH) and Progesterone levels fall. There is about 90% decline in Estradiol in the three to four years surrounding finals menses, resulting in menopausal symptoms (eg. hot flashes, night sweat, insomnia, mood changes, decrease libido) and bone loss.[4] Besides a decrease in female hormones, there is a 50% decrease in testosterone during the female's mis-reproductive life, but it will not show much change during the menopausal transition and years after menopause. Figure 1 shows the hormonal imbalance and concentration during early menopause transition and post-menopause.



Figure

Source: http://www.pathophys.org/menopause/

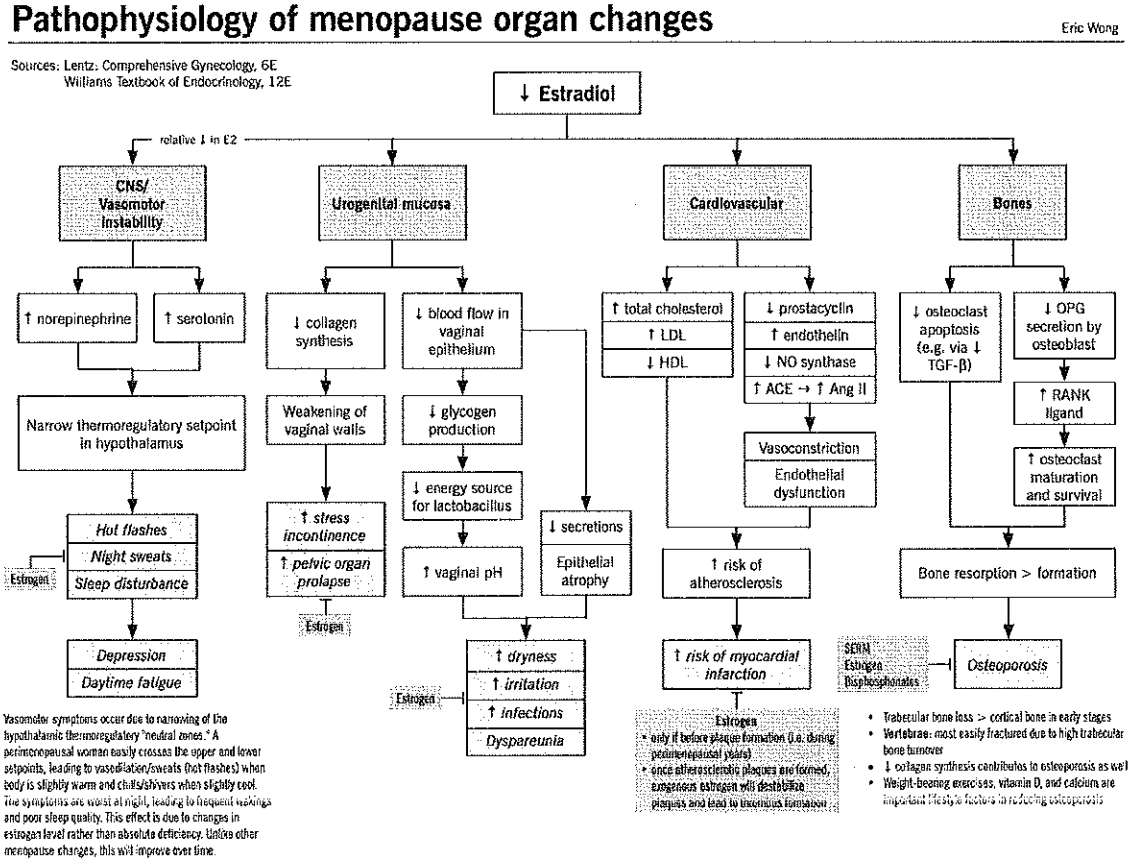
IV. Pathophysiology & Clinical Features during Menopause

Besides the classic symptoms of menopause, there are also important systemic effects that will impact the menopausal patient. Estrogen is cardio-protective due to its role in decreasing low density lipoprotein (LDL) levels and increasing high density lipoprotein (HDL) levels. Due to estrogen's low levels during menopause, a women is at high risk of developing cardiovascular diseases such as hypercholesterolemia, acute coronary syndrome, atherosclerosis and myocardial infarction. As shown in figure 1, the ovarian function declines and eventually suffers from anatomical differences like atretic follicles, small ovarian volume and lack of follicular cysts.[6] During early menopausal transition, there is fluctuant endometrial thickening due to elevated estradiol levels. At a later menopausal transition, anovulation occurs. The decrease in Sex-hormone binding globulin and progesterone will result in an elevated estrogen level thus causing an increase in proliferation of endometrial tissue. Estrogen's levels in a post-menopausal female will cause endometrial atrophy and cystic changes.

There are estrogen and progesterone receptors along the urogenital tract. Post-menopausal women experience vaginal atrophy and lack of vaginal lubrication causing dyspareunia and, sometimes, bleeding. There is an increased susceptibility to infection due to changes in vaginal pH (from 4.5 to 7). Urinary incontinence and pelvic structure prolapse increases after menopause. Soft adipose tissue replaces the dense breast tissue years after menopause. Vasomotor symptoms like hot flashes occur due to estrogen withdrawal. This withdrawal causes stimulation in norepinephrine and activation of serotonin as a result narrowing the thermoneutral zone in the thermoregulatory center. Vasodilation caused by release of neurotransmitters causes an increase in skin temperature, heart rate and blood pressure. These episodes of hot flashes usually occur at night causing sleep dysfunctions.

Menopause brings with it bone changes. It causes primary osteoporosis due to deficiency of estrogen. A decrease in estrogen causes to be more bone resorption by the osteoclasts than bone formation by the osteoblasts. In addition, loss of estrogen sensitizes the bone to have an increased response to parathyroid hormone (PTH). In a Vitamin D deficient postmenopausal female, there will be a decrease in serum calcium. In response to low serum calcium, the parathyroid gland will release PTH. Without estrogen, calcium release by the bone will be more for the same amount of PTH stimulation thus weakening the bone's structure. Estrogen's effect in vascularity (increased), sebaceous glands (increased) and collagen content (increase) will no longer occur since its level will be decreased. As a result, patients experience loss of elasticity and thinning of the skin. The above mentioned systemic effects because of decrease hormone levels during menopause are appreciated in figure 2.

Figure



Source: http://www.pathophys.org/menopause/

V. Subcutaneous Hormone Pellets

a. Advantages of pellets

The pellets are made up of either testosterone or 17B-estradiol. They are implanted subcutaneously and dissolve throughout the time. They provide a steady and consistent hormone levels when compared to other modalities of hormone replacement therapy. The amount and rate of absorption of the pellet varies depending on the implantation site and the number of pellets implanted.[5] Subcutaneous administration avoids the first pass effect of the liver, which converts oral estrogen to estrone, a weaker product hormone.

It has been studied to be superior to other forms of HRT regarding bone and cardiovascular health.[10] Overall, subcutaneous estradiol and testosterone can alleviate menopausal symptoms such as insomnia, hot flashes, palpitations, loss of libido, irritability, poor memory and decreased concentration.

b. Subcutaneous Testosterone implants

Testosterone is also referred as the male hormone and it is being used to treat symptoms of hormone deficiency in pre and postmenopausal women.[8] Although men have higher circulating testosterone than women, it is the most abundant biologically active hormone in women.[7,8] As discussed above, it is produced in the adrenal glands, ovaries and from androgen precursors. Subcutaneous testosterone implants have been shown to be a safe and effective method of testosterone delivery for over 70 years in both sexes.[7] Through a process known as aromatization, the continuous levels of testosterone provided by the implants also provides a major source of estradiol.

Testosterone normally helps maintain adequate sex drive, sperm production (in men), bone density, muscle mass, RBC production and fat distribution. A research done by Glaser et al (2015) showed that using testosterone implant actually lowered the risk of breast cancer and that none of the women with previous history of breast cancer who participated in that research had a cancer recurrence. This type of hormone replacement therapy has been shown to be a superior treatment for multiple conditions like depression, vaginal dryness, hot flashes, decrease libido/sex drive, uterine fibroids and PMS without increasing the risk of breast cancer. When testosterone is delivered subcutaneously, it does not adversely affect liver function, lipid levels, blood pressure nor serum glucose levels.[2]

Some of the indications for testosterone supplementation in addition to estradiol supplementation in postmenopausal women includes: loss of libido, fatigue, low energy, impaired memory and concentration, muscle weakness and complaints of emotions. Unwanted side effects of testosterone supplementation are dose dependent and reversible. The most common side effects are acne, hirsutism, slight enlargement of the clitoris and increased facial hair growth. Other less common side effects are reduced HDL cholesterol, deepening of the voice and polycythemia. Testosterone's therapy dosage is determined by the patient's tolerance of side effects and severity of symptoms. It comes in four different dosages: 25mg, 50mg, 75mg and 100mg.

c. Subcutaneous Estradiol implants

Since the 1930's, subcutaneous estrogen pellets have been successful for the relief of menopausal women. This biodegradable subcutaneous pellet is composed of 17B-estradiol in a compressed form, without the presence of any binder, diluent or excipient.[13] It is placed into the buttocks or abdominal wall's adipose tissue. Estradiol is biologically much more active than estrone, the main constituent of conjugated estrogens.[11] In order to avoid endometrial carcinoma due to unopposed estrogen therapy, it is used in conjunction with oral progesterone. Estradiol helps in alleviation of menopausal symptoms. Since they are subcutaneous, the hormone's level tend to be steady and consistent for at least three to five months. Estradiol also helps in the treatment of psychological disorders (eg. depression, anxiety) prevention of postmenopausal osteoporosis and offers cardio protective properties by altering lipid metabolism.

Indications for Estradiol supplementation include: symptoms of loss of ovarian function (eg. anovulation, amenorrhea), hot flashes, postmenopausal osteoporosis, vaginal atrophy, emotional stability and decreased tissue tone.[5] Contraindications for estradiol supplementation are patients with a history of thromboembolic episodes or phlebitis (eg. pulmonary embolism and deep vein thrombosis), past or present history of breast carcinoma, known or suspected estrogen-dependent breast or endometrial tumor and undiagnosed vaginal bleeding. Yimeng et al (2018) analyzed 3477 subjects and no significant association was fount between patients with HRT and risk of recurrence of breast cancer. When used in conjunction with testosterone therapy, it has shown to be protective against breast cancer.[7]

Similar to subcutaneous testosterone supplementation, this therapy has shown to be a superior treatment for the above mentioned compared to the other HRT modalities (eg. oral and injectable). Common side effects include mild temporary breast tenderness, moderate weight gain, nausea, vomiting, stomach upset, headache, changes in menstrual periods or break-through vaginal bleeding. Estradiol's therapy dosage is determined by the patient's tolerance of side effects and severity of symptoms. It comes in four different dosages: 25mg, 50mg, 75mg and 100mg.

d. Risks/complications of pellet insertion

Just like any medication and/or procedure, there is always a risk or complication involved. Although rare, subcutaneous pellet insertion can be complicated by infection of the site where pellet was implanted, hematoma of the insertion site, minor bleeding, and foreign body reaction. Complications of Testosterone and Estradiol pellets are mentioned above in section Vb and Vc.

VI. Hormone pellet cost

When comparing the cost of drugs needed to treat the individual symptoms caused by menopause (eg. medicated skin lotions, antidepressants, sleep aids, among others), as well as the monthly cost of the other forms of hormone replacement therapy, pellets are more cost effective. These pellets usually need to be inserted two to three times a year, depending on how rapidly the patient metabolizes these hormones.[1] The cost for the insertion of these pellets usually is around $275 for

women and $300 for men, but these prices tend to vary from practice to practice. They can be as low as $200s to as high as $600 USD per insertion depending on the amount of pellets needed.

VII. FDA Approval & Implantable Hormone Pellets

Implantable estradiol and testosterone pellets have been suggested as treatment for symptoms of menopause. Some third party payers have derived that this form of hormone supplementation is considered investigable, when actually the product has been used almost a century and multiple studies have proven its safety and efficacy. These implantable hormone pellets are a compound substance, just like hormone creams, gels and suppositories, made by a specialized pharmacist. They are specifically described by the United States Pharmacopeia National Formulary and FDA approval is not necessary since it is a compounded drug without the presence of any binder, diluent or excipient.

VIII. Conclusion

Hormone pellets have been used since the late 1930s for the treatment of menopausal symptoms. They have been shown to be superior to the other modalities of hormone therapy, like oral and injectable, in terms of treatment cost and providing a steady and consistent hormone level in the body for a period of months. The negative systemic effect and symptoms from menopause can be better managed by supplying a hormone deficient women with subcutaneous estradiol and testosterone pellets. They help alleviate menopausal symptoms (eg. mood changes, depression, vaginal dryness, hot flashes), increases skin collagen production, provide a cardio protective effect by lowering LDL cholesterol and increasing HDL cholesterol, and can prevent postmenopausal osteoporosis. In addition, it was shown by a study that testosterone supplementation can lower the risk and recurrence of breast cancer. This modality of hormone replacement should be discussed more frequently to women experiencing menopausal symptoms and its systemic effects since it has been well accepted and tolerated by those who have tried it.

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