Women in Balance

SCIENCE ADVISOR

SPECIAL REPORT:

Hormone Therapy for Mid-Life and Beyond

A New Perspective

Chair
Jane L. Murray, MD, Editor-in-chief

Authors and Faculty
Margaret N. Groves, M.Phil., M.Ed.R.
Kent Hermsmeyer, PhD, **Colleen Reilly,** MPA
Jerilynn C. Prior, MD, **Frank Z. Stanczyk**, PhD,
Kenna Stephenson, MD, **Helene B. Leonetti**, MD,
Deb Soholt, RN, MS

About Women in Balance

OUR MISSION

Women in Balance is a nonprofit organization dedicated to helping women achieve optimal health and wellness through hormone balance.

OUR VISION

At Women in Balance, we imagine a day when every woman has the individual tools she needs to create wellness and hormone balance in her life. In response to the growing health concerns and needs of women over the age of forty, we are building the nation's premier resource for women on wellness and balance – a resource that goes far beyond addressing disease but one that seeks to empower women to find answers to their unique health needs. We want everyone woman to feel her best, from the inside out.

Science Advisor is published by Women in Balance, Po Box 12004, Overland Park, KS 66282-2004

Hormone Therapy for Mid-Life and Beyond

A New Perspective

ABSTRACT

A number of hormonal changes take place as women move beyond their childbearing years and enter a new phase of life. Just as the body responds during puberty or pregnancy with biochemical and physiologic changes to support these states, it responds also to menopause, providing the conditions required for sustaining life in later years. Attempts to address uncomfortable or painful symptoms of menopause have resulted in some apparent risks for long term adverse health consequences, such as breast and endometrial cancer and heart disease. In response to these findings, studies of lower dose estrogen therapy begun early in menopause are underway. Hormones that are identical in molecular structure to those found in the human body, sometimes referred to as "natural" or "bioidentical" hormones, are also being used in place of nonhuman hormones because of their potentially more favorable physiologic effects.

This review begins with a synopsis of some of the reasons why women are being prescribed hormone therapy, then proposes a new way of conceptualizing the hormonal and physiologic changes women experience during the transition into midlife and beyond. It also presents research and examines multiple hormonal changes that may need to be addressed in order both to alleviate short-term symptoms, and preserve long-term health.

WHY ARE WOMEN BEING PRESCRIBED HORMONE THERAPY (HT)?

In 2005, a report prepared by the Oregon Evidence-Based Practice Center and published by the U.S. Agency for Healthcare Research and Quality (AHRQ) reviewed the history and current status of menopause symptomatology and its treatment (Nelson 2005). The extensive report was based on published studies (in English) of menopause symptoms and evaluated randomized, controlled clinical trials of various treatment regimens. The authors rated the quality of these studies prior to drawing conclusions from them. This rating system included a meta-analysis of results from cohort studies meeting their inclusion criteria.

Conclusions from this major review noted that the symptoms most consistently associated with the menopausal transition were vasomotor symptoms (hot flashes and night sweats) and vaginal dryness, and that as far as the large variety of treatments for menopausal symptoms are concerned, only estrogen therapy is conclusively associated with benefit (although the authors stated that other therapies may prove effective if further studied). This report, along with scientific evidence presented at a National Institutes of Health-sponsored State of the Science Conference on Management of Menopausal Symptoms in March 2005, formed the basis for an independent panel to prepare a state-of-the-science statement on management of menopause-related symptoms [National Institutes of Health (NIH), 2005].

The NIH statement clearly defined a need for the "demedicalization" of menopause and promoted the recognition of menopause as a normal, healthy life transition. However, in cases where symptoms are especially severe, particularly in women who have undergone bilateral oophorectomy with its resulting sudden loss of ovarian function, hormonal supplementation is often necessary. The statement described many of the "alternative" methods available for treatment, but was unable to evaluate their efficacy because of a lack of large controlled trials.

Estrogen deficiency in the perimenopausal period has been assumed to be the primary cause of menopausal symptoms. Additionally, a prominent justification for long-term hormone therapy has been the idea that estrogen replacement would also protect women from developing conditions in later life that have also long been attributed to low estrogen levels, such as cardiovascular disease and osteoporosis.

Observations that coronary heart disease (CHD) is the leading cause of death in postmenopausal women, and that premenopausal women incur a lower rate of CHD than do men, and since estrogen levels decline after menopause, a logical conclusion has been to prescribe estrogen therapy as a means to prevent the development of CHD in postmenopausal women. A landmark meta-analysis and systematic review of existing HT studies designed to assess the risks and benefits of long-term HT for asymptomatic postmenopausal women (Grady et al, 1992) supported the assertion that such therapy was beneficial, concluding that reductions in heart disease and hip fracture incidence outweighed the increased breast and endometrial cancer risk with HT. More recently, Stefanick (2005) has described in detail the history of estrogen and other hormonal therapies as potential solutions for several women's health issues.

The long-standing opinion that supplementation with estrogen in order to reduce cardiovascular risk and the occurrence of fractures was tested in a series of large, randomized, placebo-controlled trials, primarily the Women's Health Initiative (WHI) study and the Heart and Estrogen/Progestin Replacement Study (HERS). The results of these and other trials over the last 10 years have recently been evaluated (Barrett-Connor 2005) with the conclusion that, contrary to previous observational studies, a reduction in CHD was not seen in the large cohort studies designed to test this hypothesis. The HERS study of conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) found no cardiovascular benefit (Hulley 1998). Additionally, there was an increase in the incidence of stroke and blood clots in the WHI study also using CEE/MPA which was abruptly halted because of this finding, together with a slightly increased incidence of breast cancer, after a mean 5.2-year follow up.

The authors concluded that this treatment regimen should neither be initiated nor continued for primary prevention of CHD (Rossouw 2002). After an average follow-up of 6.8 years, the WHI CEE-

only trial for postmenopausal women who had undergone a hysterectomy was also stopped because of an increased risk of stroke and a lack of overall benefit, but in this treatment group there was no increase in breast cancer (Anderson 2004).

Barrett-Connor (2005) and others (Prestwood 2003, Ettinger 2004) have proposed that a reduction in dosage of HT would be a possible means of overcoming adverse cardiovascular and carcinogenic effects of such therapy while maintaining the overall benefit to women in terms of fracture prevention. No long term studies as yet support this recommendation.

Estrogen therapy, typically CEE, is still considered standard by the North American Menopause Society (NAMS 2005) and the American College of Obstetricians and Gynecologists (ACOG) for short-term relief of hot flashes and vasomotor symptoms. The results of two large studies currently underway will help to resolve the question of whether short term estrogen therapy started early in the menopause transition for relief of these symptoms will also help protect women from cardiovascular disease later in life. These studies include the Kronos Early Estrogen Prevention Study (KEEPS) and the Early Versus Late Intervention Trial with Estradiol (ELITE).

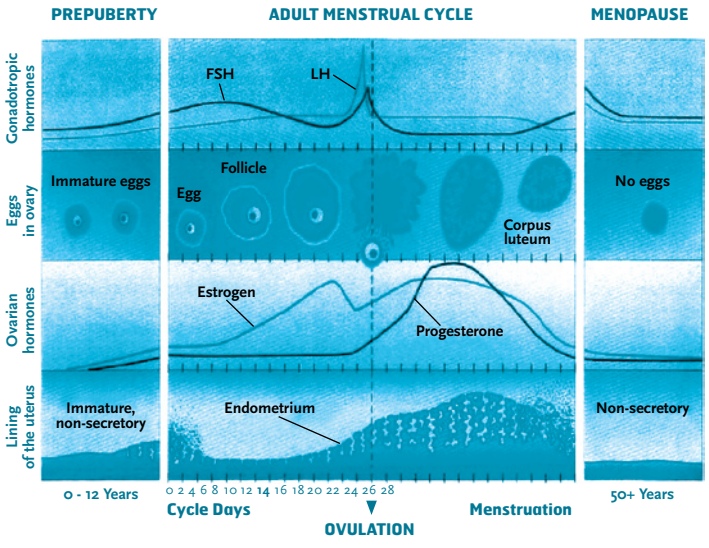
WHAT HORMONAL CHANGES ARE OCCURRING DURING THE MENOPAUSAL TRANSITION?

Estrogen and Progesterone

One major aspect of treatment of menopause-related symptoms has been the emphasis on estrogen deficiency as the cause of both short- and long-term health issues in menopause, but is this really the only issue for all women? Prior (1998) carried out a major review of the endocrinology of perimenopause and found that, rather than low estrogen levels, this stage is characterized by erratic but on average *higher* estrogen levels than found premenopausally. High estrogen levels are also correlated with intensity of symptoms in women with severe pre-menstrual syndrome and abnormal scores on psychometric tests during menopause, indicating that much of the symptomatology of early menopause (in terms of vasomotor symptoms, breast tenderness, menorrhagia and mood changes) may be a result of higher, rather than lower, estrogen.

In menstruating perimenopausal women making daily records of menopausal symptoms, night sweats and breast tenderness were most commonly experienced in the premenstrual phase (Hale 2003), challenging the popular belief that hot flushes and night sweats are related to low estrogen levels, since estradiol levels rise prior to menstruation. Prior (2006a) discusses therapeutic implications of these observations for the hormonal changes needing to be addressed in the perimenopausal transition.

Consider the function of the hormones in the normal reproductive cycle. Estrogen causes the uterine lining to proliferate in preparation for implantation of a fertilized egg, and it stimulates a number of physiological events designed to prepare the body for pregnancy, such as stimulation of protein and lipid synthesis and mitotic activity. Progesterone levels rise after ovulation and act to complete the preparation of the uterus for implantation, resulting in increased secretory activity and strengthening of the vasculature. When progesterone becomes the dominant hormone in the secretory (luteal) phase of the menstrual cycle, it reduces the estrogen-binding capacity of the endometrial tissue. If implantation does not occur, progesterone levels fall and the endometrial lining is shed in the menstrual flow. If implantation does occur and pregnancy results, progesterone levels remain high to support the conditions required by the developing fetus. Indeed, the consistently high



physiologic progesterone levels seen in pregnancy would indicate that progesterone is safe as a therapeutic agent, and indeed it is used in women with infertility problems due to luteal progesterone insufficiency in order to raise circulating and endometrial progesterone levels to those of the normal luteal phase.

Prior (1998) notes that progesterone levels are declining during perimenopause as the number of anovulatory cycles increases, since progesterone levels would normally rise in response to ovulation. However, few studies have adequately documented the changes in progesterone through the transition. Nevertheless, the use of progesterone is sometimes used alone to relieve menopausal symptoms, and the results of such studies are discussed later in this review.

The terms "progestin"and "progesterone"are often interchanged, but it is important to distinguish between the two because they have very different safety profiles and physiologic properties. Progesterone is the molecule produced by the human body while the various progestins are chemically altered progesterone-like molecules that can be patented. Therefore, progesterone that is identical to the molecule in the human body has often been referred to as "natural" or "bioidentical" progesterone. The molecular and pharmacokinetic differences between various progestins and progesterone have been described by Stanczyk (2003). The term "natural" has been a source of confusion, many patients and clinicians believing that "natural" refers to progesterone of plant origin. While progesterone is normally manufactured from the diosgenin found in wild yams, a chemical process in the laboratory converts it into the progesterone molecule that is identical to the endogenous biological form, and is thus "bioidentical". Unprocessed wild yam creams do not contain progesterone and the body cannot make progesterone from them when applied. In this review, the word "progesterone" consistently refers to human isomolecular progesterone only.

...progesterone that is identical to the molecule in the human body has often been referred to as "natural" or "bioidentical" progesterone.

Androgens

More researchers are evaluating androgen deficiency in women (Miller 2001), as levels of dehydroepiandrosterone (DHEA) and testosterone fall steadily with age and can contribute to some of the symptoms seen in menopause. This area of hormone research promises to offer much needed information to clinicians and the women they treat.

Androgen therapy with DHEA or testosterone has been found to restore sexual function, particularly in women who have experienced a sudden drop in androgen levels, such as younger women undergoing surgical menopause, or women with adrenal insufficiency (Arlt 2006). DHEA has been found to successfully restore sexual function in older women and has had a good safety profile, even after 50 mg/day oral DHEA was administered for one year as found in the DHEAge study, which also found an increase in BMD with DHEA treatment in women over 70 years old (Baulieu 2000). Labrie (2005) has suggested the use of DHEA for physiologic hormone replacement because of its nature as a hormone precursor, producing estrogens and testosterone in the hormone-dependent target tissues precisely according to local needs, and thus alleviating many of the symptoms of hormone deficiency while avoiding the systemic side effects of exogenous hormone therapy. The authors call this new concept "intracrinology" as opposed to endocrinology, and suggest that it offers new options for menopausal women. Arlt (2006) has reviewed the use of androgen therapy in women and concluded that it should be reserved for women with severe androgen insufficiency. Certainly more studies and longer term studies of androgen therapy are needed.

Vitamin D

Commonly called a "vitamin", vitamin D is actually a hormone since it is formed through the action of sunlight on its precursors in one organ (the skin) and exerts wide-ranging physiologic effects on other organs throughout the body. It is currently the subject of much study because its deficiency is widespread, particularly in the elderly.

Researchers have described the widespread implications of vitamin D deficiency for health, including not only various cardiovascular diseases and osteoporosis, but also links with types 1 and 2 diabetes, cancer, some autoimmune diseases and multiple sclerosis

An estimated 70% of women aged 65 have vitamin D deficiency and 90% of women aged 75 are deficient (Moore 2004). Vitamin D deficiency results in an increase in parathyroid hormone levels that can lead to the bone loss and cardiovascular disease commonly observed in postmenopausal women. Researchers have described the widespread implications of vitamin D deficiency for health, including not only various cardiovascular diseases and osteoporosis, but also links with types 1 and 2 diabetes, cancer, some autoimmune diseases and multiple sclerosis (Holick 2005a, 2005b, 2006, Peterlik and Cross 2005, Zittermann 2003).

The epidemic levels of vitamin D deficiency even in the general population may be largely attributable to limited exposure to sunshine and possibly to overuse of sunscreen products, because of the concern about skin cancer with sun exposure. Need et al (1993) studied levels of serum 25-hydroxyvitamin D [25(OH)D] in postmenopausal women and found that these were positively related to hours of sunlight during the preceding 2 months and to skinfold thickness on the back of the hand, and inversely related to body mass index. They attributed the age-related decline in 25(OH)D levels to the reduction in skin thickness seen with aging, and it has been suggested that the amount of vitamin D precursors present in the skin may also decline with age. The reduction in vitamin D levels in people with more body fat is probably due to the retention of vitamin D by the fat tissue, from which it is not easily mobilized.

As far as hormone replacement is concerned, an updated view should encompass the concept of evaluating the range of hormones affected at midlife and seeking hormone balance, considering a variety of deficiencies that may need to be supported for optimal health and prevention of long-term morbidity. The concept of only "estrogen replacement" is proving to be inadequate and ignores the impact of the depletion of other hormones on postmenopausal functioning.

PERIMENOPAUSAL SYMPTOMS

Vasomotor Symptoms

Hot flashes and night sweats are reported by at least 50% of women (Nelson 2005) in the perimenopausal period. These are caused by fluctuations in hormone levels in early perimenopause and subside thereafter, but their incidence also correlates significantly with anxiety levels (Freeman 2005). While estrogen therapy has been found to be of benefit, many women are rejecting hormone therapy because of the publicity surrounding the negative results of the WHI study. There is also much evidence for a strong placebo effect when alternative therapies have been studied. Women who find an herbal remedy that seems effective may be advised to continue its use, although trials have had conflicting results as to its efficacy (North American Menopause Society 2004).

Progesterone cream alone has been found to improve vasomotor symptoms in two small studies. In one, 25 of 30 (83%) symptomatic women using 20 mg/day progesterone cream reported symptom relief compared with 5 of 26 (19%) using placebo cream (Leonetti 1999). Stephenson (2004) also observed a significant reduction in Greene Climacteric Scale scores with 20 mg/day progesterone cream treatment compared with placebo in 30 healthy, symptomatic postmenopausal women in a randomized, double-blind, crossover study. However, there are few published studies of progesterone for relief of menopausal symptoms, and some have found no benefit (Wren 2003). Progesterone is widely available over the counter as a transdermal cream, and as prescription capsules and a vaginal gel. Compounding pharmacies can provide progesterone in the form of sublingual troches and drops, vaginal suppositories and topical creams upon a clinician's prescription.

A study is underway in Canada using micronized oral progesterone versus placebo, and examining its effects on vasomotor symptoms, forearm blood

flow, lipid levels, and blood pressure in menopausal women with no cardiovascular risk factors who are experiencing moderate to severe vasomotor symptoms . Completion is expected in 2008.

Vaginal Atrophy and Reduced Libido

It is frequently assumed that urogenital symptoms such as vaginal dryness and atrophy are a natural consequence of low estrogen levels. But studies of non-hormonal vaginal moisturizers consistently show that these products effectively alleviate symptoms and improve signs of atrophy (Bygdeman and Swahn 1996, Morali 2006, Nachtigall 1994, Parsons 2003, van der Laak 2002), and are often recommended as appropriate alternatives to systemic or local estrogen therapy in symptomatic women (Bachmann and Nevadunsky 2000, Society of Obstetricians and Gynaecologists of Canada 2005).

Another common observation is that various aspects of sexual function decline during and after the menopause transition, and vaginal symptoms can directly result from sexual arousal problems (Laan and van Lunsen 1997). Women with decreased libido are more likely to report vaginal dryness and depressive symptoms (Gracia and Freeman 2004). There can be many possible contributing factors to the overall loss of libido, including reduction in androgen levels, poor body image due to weight gain and/or aging, stress, use of anti-depressants and declining sexual interest by the woman's partner.

Population-based studies show that women's sexual function declines with increasing age starting even in the 30s (Hayes and Dennerstein 2005), but a marked decline in sexual interest and frequency occurs after menopause (Dennerstein and Hayes 2005). Studies of sexuality in postmenopausal women indicate that hypoactive sexual desire is related to sexual responsiveness and to partner relationship satisfaction, and is more prevalent in surgically menopausal than naturally menopausal women (Dennerstein 2006). Androgen deficiency is particularly observed after surgical menopause and in patients with poor adrenal function, and is clinically associated with loss of libido, reduced energy and poor sexual responsiveness. Physiological menopause, on the other hand, is not necessarily associated with androgen deficiency (Arlt 2006). Prior levels of sexual functioning and relationship-related factors have been found to be more significant determinants of sexual function than estradiol levels in naturally menopausal women (Dennerstein 2005). In the Massachusetts Women's Health Study, menopause status was less important than relationship factors and physical and mental health factors as a determinant of sexual function (Avis 2000). Sexually active women (including those who masturbate) have less vaginal atrophy than sexually inactive women and also have higher levels of androgens (Leiblum 1983). Regular sexual activity helps maintain vaginal health (Bachmann and Nevadunsky 2000, Society of Obstetricians and Gynaecologists of Canada 2005).

LONG TERM HEALTH ISSUES IN POSTMENOPAUSAL WOMEN

Bone Loss/Osteoporosis

Bone loss, leading to reduced bone mineral density (BMD) and eventually osteoporosis, is the result when osteoclast-mediated bone resorption and osteoblast-mediated bone formation become unbalanced. In the normal state, the bone is in a state of homeostasis in which bone is formed at the same rate as it is resorbed (i.e., broken down to release calcium into the bloodstream, which is a mechanism for maintaining blood calcium levels), referred to as "bone turnover". Hormones play a significant role in these processes and therefore alterations in bone can occur in the postmenopausal period.

Estrogen and Progesterone

Estrogens have been prescribed as HT for the prevention of bone loss because of the known effect of estrogen on inhibiting bone resorption. The incidence of long-term adverse effects with estrogen therapy has led to recommendations for a reduction in estrogen dosage, and a study of 0.25 mg/day oral estradiol versus placebo for three years in women over 65 years old (with 100 mg/day oral micronized progesterone in women with a uterus in both groups) found an increase in BMD in the estradiol group compared with placebo (Prestwood 2003), although the number of subjects was relatively small (83 in the estradiol group and 84 in the placebo group).

In the perimenopausal period, bone turnover is still high, but this slows with time as the body adjusts to the lower hormone levels available. Despite higher average estradiol levels in the perimenopausal period, significant spinal bone loss is seen during this time. Serial assessments of bone changes and fracture in the 7000 women being followed longitudinally in the Canadian Multicentre Osteoporosis Study will shed more light on the complicated pathophysiology of osteoporosis as women enter menopause.

It is important to note that the biochemical mechanisms by which various hormones exert their effects on bone are complex, and their inter-relationships have not been fully elucidated. Estrogens and androgens are thought to protect against bone loss mainly by reducing the rate of formation of osteoclasts and osteoblasts, thereby slowing bone resorption (Manolagas 2002). Evidence for the bone-trophic activity of progesterone, acting interdependently with estrogen, has been reviewed by Prior (1990). The enhancement of bone formation by progesterone could explain the decrease in spinal bone density observed in premenopausal women with ovulation disturbances and low endogenous progesterone levels, irrespective of their levels of physical activity (Prior 1990). Also, in the population-based Michigan Bone Health Study, those premenopausal women in the lowest tenth percentile for peak bone mass had the highest rates of luteal phase insufficiency (i.e. progesterone deficiency) as shown by urinary pregnanediol glucuronide levels, in addition to lower than normal estrone-3-glucuronide levels (Sowers 1998). Cyclic administration of MPA increased spinal bone density significantly in a 1-year study of 61 premenopausal women with ovulatory disturbances. Calcium supplementation also increased bone density but not significantly (Prior 1994). The relative roles of estrogen and progesterone in postmenopausal bone changes have been reviewed by Lee (1994 and 2004).

The effects of progestagens and estrogen are synergistic and complementary to each other, as indicated by clinical trials that have found greater increases in spinal BMD when MPA is added to CEE than with CEE alone (Lindsay 2002, Writing Group for the PEPI Trial 1996). However, fracture risk data for CEE and CEE/MPA were compared only with their respective placebo groups in the WHI study, therefore a direct comparison of the two treatment groups is not easy. The wide variation in progestin and progesterone formulations has hindered the statistical power of meta-analyses to detect the effects on BMD of the progesterone/progestin component of HT, but tibolone (a progestin widely used in Europe but not approved in the US) was shown to have similar effects on BMD to any estrogen compound in one meta-analysis (Dören 2003).

It is probable that the anti-resorptive properties of estrogen are more important in the early years after menopause when the rate of bone turnover is high. This effect is especially apparent in the case of premenopausal oophorectomy with sudden loss of ovarian hormone production. In a 1-year randomized study of 0.6 mg/day CEE versus 10 mg/day MPA in premenopausal women (aged 45 +/- 5 years) oophorectomized for benign diseases, CEE suppressed high levels of bone resorption but MPA did not in the 33 women who completed the study (Prior 1997). Transdermal progesterone's effect on bone density may be dependent upon timing of use in the peri- and postmenopause. A study by Leonetti (1999) showed no improvement in BMD within five years of menopause when subjects were likely to be in a phase of high bone turnover. In that study, the doses of progesterone used were very low (20 mg transdermally twice a day). Longer term and larger studies with progesterone are needed to show potential benefit of progesterone for maintenance of bone density. Two hundred women aged at least 70 years are being recruited for a study of BMD before and after transdermal progesterone use, and will help answer this question.

Preliminary data show that continuous, rather than cyclic, progesterone or MPA therapy may be required in menopausal women in order to show a gain in bone (Prior JC, unpublished observation). The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, which only used cyclic progesterone or progestin therapy, found no benefit in continuing HT beyond three years in terms of additional bone gain (Greendale 2002), further confirming the only shorter-term benefits of estrogen therapy.

Vitamin D

The implications of vitamin D deficiency for postmenopausal bone loss leading to osteoporosis have been widely researched and are a significant factor in the pathogenesis of this condition. Current estimates are that, on average, 64% of postmenopausal women with osteoporosis are vitamin D deficient (Rizzoli 2006), with a higher prevalence in non-equatorial regions. Inadequate vitamin D leads to reduced calcium absorption resulting in a decrease in serum calcium: when levels of 25-hydroxy vitamin D [25(OH)D] fall below 32 ng/ml, an increase in parathyroid hormone (PTH) production is stimulated (Need 2004), which acts to mobilize calcium from the bone in order to maintain serum levels of calcium. Dietary calcium intake is also a significant factor, since this contributes to the maintenance of serum calcium, and studies have shown a significant benefit for BMD when dietary calcium is increased (Aloia 1994). Absorption of dietary calcium from the intestine also depends on adequate vitamin D levels. Holick (2005) examined serum 25(OH)D and PTH levels in 1500 postmenopausal women receiving osteoporosis therapy (either for prevention or treatment). Despite the fact that 60% of the women were taking vitamin D supplements of at least 400 IU/day, over half had vitamin D insufficiency (serum levels of 30 ng/ml or less) resulting in elevated PTH levels and a 15% incidence of secondary hyperparathyroidism. Among women with less than 9 ng/ml 25(OH)D in the serum, there was a 75% prevalence of secondary hyperparathyroidism.

Current estimates are that, on average, 64% of postmenopausal women with osteoporosis are vitamin D deficient.

Another important aspect of vitamin D insufficiency is that it reduces muscle strength, which can lead to a higher risk of falling (Holick 2005b). Clearly the combination of osteoporosis and an increased risk of falling is a recipe for fractures. This concern is apparent from a meta-analysis (Bischoff-Ferrari 2005) of vitamin D intake and fracture incidence: high doses (700 – 800 IU/day) of vitamin D were associated with a significant relative risk reduction of 26% for hip fracture and 25% for nonvertebral fracture, while doses at the current RDA of 400 IU/day resulted in a non-significant, but nonetheless detectable, risk reduction. The authors conclude that 400 IU/day is insufficient vitamin D to prevent fractures.

Bispohospanates and SERM's

In an attempt to simulate the anti-resorptive effects of estrogen, drugs such as the selective estrogen-receptor modulators and the bisphosphonates have been used. These drugs require long term evaluation and already some safety issues, such as osteonecrosis of the jaw with bisphosphonates (Woo 2006) are emerging, and combination therapy with either estrogen or anabolic agents plus bisphosphonates is controversial (Binkley and Krueger, 2005). Although these pharmacotherapeutic interventions can substantially reduce fracture risk in addition to calcium and vitamin D supplementation alone, they are recommended mainly for patients at very high risk for fractures and only for a short time, i.e., less than a year (Gass and Dawson-Hughes 2006).

Cardiovascular Disease

The Centers for Disease Control (CDC) data for 2001-2003 shows cancer of all types as the leading cause of death for women between the ages of 35 and 74, but by age 75 cardiovascular disease becomes the leading cause of death, overtaking all cancer; this trend continues to rise with age. There are wide variations in cardiovascular disease incidence in countries throughout the world and, although men have consistently higher disease rates than women, further epidemiological study is required to elucidate cultural, dietary and hormonal alterations that could account for this difference.

As discussed previously, earlier assumptions that the relatively higher cardiovascular disease rate in men than in women can be attributed to the fact that men have lower levels of estrogen than women have been largely debunked by the increase in cardiovascular problems seen when long-term estrogen therapy is given (Ouyang 2006). Even before the WHI trial results were known, a pooled analysis of existing HT trials (Hemminki and McPherson 1997) showed no benefit with HT

in terms of cardiovascular disease prevention. However, the adverse cardiovascular outcomes in the WHI study may have been related to the length of time after menopause when estrogen therapy was used, since the women in the WHI study were an average of 63 years old when they started HT and those at the younger end of the age range in fact had fewer adverse cardiovascular events (Manson 2003).

Animal experiments have been used to demonstrate a beneficial cardiovascular effect of estrogen, and researchers have called for clinical testing of the new hypothesis that early initiation of estrogen therapy will delay the development of atherosclerosis and possibly lead to better cardiovascular outcomes (Miller 2005). In the Kronos Early Estrogen Prevention Study (KEEPS) 720 women early in menopause are being followed using lower estrogen doses (0.45 mg/day oral CEE or 0.05 mg/day transdermal estradiol) in combination with cyclic oral micronized progesterone 200 mg/day for 12 days per month, compared with placebo to evaluate several cardiovascular risk factors. Completion of the study is expected in 2010. Also, the Early Versus Late Intervention Trial With Estradiol (ELITE) is a study of 504 women either less than 6 years or 10 years or more years after menopause. Participants are randomized to receive either 1 mg/day oral estradiol or placebo (with 4% vaginal progesterone gel or placebo respectively for 10 days each month in women with a uterus) and cardiovascular outcomes measured.

Studies have shown progesterone's profound effect on coronary artery reactivity as distinct from the benefits of progesterone for vasomotor symptoms discussed earlier. Progesterone alone, even without estrogen, has a major protective effect of decreasing coronary reactivity in rhesus monkeys (Miyagawa et al, 1997a). Furthermore, in pre-atherosclerotic, oophorectomized rhesus monkeys fed a high fat diet, the beneficial protective effect of transdermal progesterone in preventing coronary hyperreactivity was even more profound than in non-atherosclerotic animals studied previously (Hermsmeyer et al, 2004). These studies suggest that the suppression of thromboxane receptor expression, which may underlie coronary, carotid, and cerebral vascular hyperreactivity, is the mechanism by which progesterone exerts its beneficial effects.

Perhaps the underlying pathogenic mechanism for coronary artery disease and stroke, the leading cause of death in women, has similar origins to the vasomotor symptoms that must also be addressed during menopause. The serious risk posed by inattention to cardiovascular deterioration in women has been recognized by the Women's Ischemic Syndrome Evaluation (WISE) study of the NIH (Johnson 2004).

Vitamin D deficiency also carries cardiovascular implications. Norman and Powell (2005) have reviewed the biochemical and genomic effects of vitamin D that have a significant impact on the properties of peripheral arteries, and discussed the paradoxical association between arterial calcification and osteoporosis. Medial layer calcification in aging arteries has been found to be a predictor of cardiovascular mortality and lower limb amputation in type 2 diabetes. Serum vitamin D levels also correlate inversely with coronary artery calcification. The role of vitamin D in the maintenance of calcium and phosphate homeostasis accounts for its importance in a variety of tissues that are dependent on calcium balance, and the relationship between osteoporosis and cardiovascular morbidity and mortality has not gone unnoticed (Nawroth 2003), arteriosclerosis being associated with osteoporotic bone loss. A recent study reported a high prevalence of vitamin D deficiency in stroke patients (Poole 2006), which may be attributable to the association between hyperparathyroidism and hypertension (Sato 2003). Somjen (2005) identified the expression of 25(OH)D-1α-hydroxylase in vascular smooth muscle cells, which converts 25(OH)D into the active 1,25-dihydroxy form of vitamin D, and its upregulation by parathyroid hormone, which can explain the vasodilatory effects of PTH. Zittermann (2005) has reviewed data supporting the hypothesis that the increasing incidence of cardiovascular disease worldwide is related to vitamin D insufficiency.

Cancer

Breast cancer is the leading cause of cancer death in women up to age 54 (in the 45-54 age group breast cancer represents 26.3% of all cancer deaths). However, in the 55-64 age group, the percentage of cancer deaths represented by breast cancer has declined to 18.5% and has been overtaken by lung

cancer deaths, which now represent 28.9% of all cancer deaths (see Table 1; figures calculated from the CDC data for 2001-2003). As is evident from the table, the percentage of cancer deaths due to lung cancer continues to rise while the percentage due to breast cancer continues to fall.

In the 55-64 age group, the percentage of cancer deaths represented by breast cancer has already declined to 18.5% and has been markedly overtaken by lung cancer deaths, which now represent 28.9% of all cancer deaths.

Evidence is emerging that a significant proportion of lung cancers are estrogen and/or progesterone receptor positive. Ganti (2006) found a highly significant association between a lower median age at lung cancer diagnosis and a shorter median survival time in women who had used HT for at least 6 weeks prior to diagnosis, compared to women who did not use HT, in 500 female lung cancer patients.

The effects of HT on survival were more pronounced in women with a history of smoking. Siegfried (2006) postulates that this finding is consistent with the tumor-promoting effects of HT, but also suggests that the progesterone or progestin component of HT may have protected women against lung cancer, and this may have masked the cancer-promoting effects of estrogen in clinical trials. She also suggests a role for progesterone therapy in the treatment of lung cancer. Ishibashi (2005) found progesterone receptors in 106 of 228 (46.5%) non-small-cell lung cancers in humans. Proliferation of receptor-positive tumor cells from these human specimens injected into nude mice, as well as in vitro, was dose-dependently inhibited by progesterone. The study also showed a significantly better clinical outcome in the progesterone receptor positive patients, which is interesting in light of the fact that tissue concentrations of progesterone and progesterone-synthesizing enzymes, indicating local progesterone production in the tumor tissue in situ, correlated with progesterone receptor status. It is notable that the majority of non-small-cell lung cancers are found in the postmenopausal age group, when endogenous serum progesterone levels are very low.

Dr. K. Albain, a lung cancer specialist at Loyola University Health System, is evaluating newly diagnosed lung cancer patients to examine hormonal factors that may explain why lung cancer behaves differently in men and women and in smokers and non-smokers (Neergaard 2006). The role of estrogens and progesterone in lung cancer is beginning to be a focus of research in the most significant cause of cancer death in postmenopausal women.

Levels of endogenous estrogens and androgens are known to be related to breast cancer risk (Key at al. 2002), and there is considerable evidence that both endogenous estrogen and the estrogens used in HT are causally related to breast cancer (Colditz 1998). Unlike estrogen, progesterone has been observed to have antiproliferative properties. The primary reason for prescribing progestins or progesterone to women with an intact uterus who

Table 1. *Percentage of cancer deaths represented by lung and breast cancer with age.*

Age group	Lung cancer as a % of all cancer deaths (women)	Breast cancer as a % of all cancer deaths (women)
35 – 44	13.8	30.6
45 – 54	20.3	26.3
55 – 64	28.9	18.5
65 – 74	31.9	13.1
75 – 84	26.3	12.0

are receiving estrogen therapy has been to protect the endometrium from estrogen's proliferative effects and the potential for development of endometrial cancer.

After the WHI trial was stopped, it was widely reported that the patients receiving combined treatment with estrogen and progestin had a higher incidence of breast cancer than the group receiving estrogen alone. However this is a misleading observation since the characteristics of the two groups were different (Stefanick 2003); also, the estrogen-only group by definition had undergone a hysterectomy, and it is known that women who have had pelvic surgery have a significantly reduced risk of breast cancer (Kreiger 1999).

The role of estrogens and progesterone in the etiology of lung cancer is beginning to be a focus of research in the most significant cause of cancer death in post-menopausal women.

In contrast to the WHI findings, a recent analysis by Chen (2006) found an increased risk for invasive breast cancer with long-term use of unopposed estrogen therapy. Endogenous progesterone levels were found **not** to increase breast cancer risk in the first study to investigate this issue in postmenopausal women; this finding was true even for progesterone receptor positive tumors, which were the most strongly affected by all circulating steroid hormones measured except for progesterone (Missmer 2004). On the other hand, higher levels of endogenous estrogens and androgens were significantly correlated with increasing breast cancer incidence.

There is evidence that women with progesterone deficiency have a markedly increased incidence of breast and other cancers (Cowan 1981), and also that the application of progesterone cream to the breasts decreases proliferative activity in breast tissue while estradiol cream increases such activity (Chang 1995). In a study of women undergoing breast tumor excision, those who had higher levels of circulating progesterone at the time of excision had a significantly improved prognosis, the authors concluding that the tumor tissue was not in an actively proliferating state at the time of excision because of progesterone's antiproliferative effects (Mohr 1996).

NEW HORMONE REPLACEMENT OPTIONS

The various hormone deficiencies outlined in this paper relate to some or all of the short- and long-term symptomatology of peri- and postmenopause described above. Many women are able to tolerate the vasomotor and urogenital symptoms occurring in the early menopausal period without medical intervention. However, because women are enjoying longer lives than they did in the past, long term consequences of hormonal imbalance may affect quality of life and even disease prevention. The hormones discussed in this review have far-reaching physiologic functions and their replacement may produce significant quality of life benefits for the aging woman. Because of ongoing controversy surrounding estrogen therapy, which is already widely covered in the current scientific literature and is the subject of much current research, the other hormones that have a significant impact on mid-life health are considered in more detail below.

Progesterone

Progestins as well as progesterone have been routinely prescribed together with estrogens in HT because of their protective effect on the endometrium, long known from in vitro and in vivo studies. Estrogen-only (also known as "unopposed" estrogen) therapy is only prescribed to women who have had a hysterectomy and are therefore at no risk of developing endometrial cancer. One problem with evaluating progesterone therapy for endometrial protection is that the ability of progesterone to counteract estrogen's proliferative effect is dependent on the dose of estrogen used, and this may explain the results of a study by Vashisht (2005) in which a massive 1 mg/day of estradiol was given transdermally: while having some oppositional effect on the proliferating endometrium, 40 mg/day of transdermal progesterone was insufficient to fully attenuate this amount of estrogen's mitogenic effect. Yet Leonetti (2003a, 2005) found 20 mg of progesterone cream twice daily to be as effective as usual doses of oral MPA in counteracting the proliferative effect of 0.625 mg/day oral CEE.

Anasti (2001) and Leonetti (2003b) also demonstrated similar antiproliferative effects on the endometrium by progesterone cream and progesterone vaginal gel in women receiving 0.625 mg/day oral CEE, the topical progesterone cream being preferred by subjects in the study. Casanas-Roux (1996) observed typical proliferative changes in the endometrium with estrogen therapy but only secretory transformations when progesterone vaginal gel was given concomitantly with oral estrogen. Cicinelli (2002) found 45 mg/day progesterone in a vaginal gel sufficiently protected the endometrium from proliferation in women receiving 0.05 mg/day transdermal estradiol. Ferrero (2002) found that transvaginal micronized progesterone (100 mg/day for 12 days/month) effectively promoted a functional, secretory endometrium, while cyclic oral MPA or transdermal norethisterone acetate more often produced endometrial atrophy in women receiving continuous transdermal estradiol. A progesterone-releasing intra-uterine device has even been found effective in the treatment of early endometrial cancer (Montz 2002), and a vaginal progesterone cream produced complete regression in 67 of 78 (90.5%) premenopausal women with benign endometrial hyperplasia (Affinito 1994).

A 2% transdermal progesterone cream was found to significantly increase skin elasticity and firmness compared to placebo cream in peri- and postmenopausal women, suggesting an additional benefit of anti-aging skin properties of progesterone cream. Despite demonstrable rises in serum progesterone levels, no side effects were seen (Holzer at al. 2005). However caution is warranted against the over-use of progesterone cream for cosmetic purposes since progesterone has a wide range of physiologic effects and the longer term consequences of dosing beyond the 40 mg/day maximum commonly used are unknown and should be evaluated by further research studies.

Transdermal or transvaginal delivery of progesterone in a cream or gel obviates side effects that may result from first-pass metabolism through the liver after oral dosing, and overcomes the problem of progesterone's short half-life when administered orally. Significantly lower amounts of progesterone are needed with a transdermal delivery system. However, some clinicians prefer oral micronized progesterone over transdermal delivery because of its tendency to induce drowsiness and thus aid sleep, which can help women who are troubled with sleep disturbances during the menopause transition.

The studies cited above have reported no side effects of progesterone given transdermally and no effects on the blood lipid profile. Hermann (2005) found that similar *whole blood* levels of progesterone were achieved in postmenopausal women receiving 40 mg progesterone cream twice a day for 12 days as were achieved with 200 mg oral micronized progesterone daily for 12 days. However, some investigators have concluded that because *serum* levels of progesterone are low after transdermal administration of progesterone that transdermal application is inadequate. Research in the area of appropriate testing methods applied to varying delivery systems is needed.

Several investigators have recorded significantly higher levels of progesterone in saliva compared with serum, plasma, or urine after application of progesterone cream (Lewis 2002, O'Leary 2000, Wren 2000), but have speculated variously as to the reasons for this. O'Leary concluded that the salivary levels confirmed the absorption of progesterone despite the lack of change in serum levels; Wren claimed that the discrepancy showed salivary progesterone to be of no value in managing therapy in postmenopausal women and that the preparation they used also had no protective effect on the endometrium (although they were attempting to counteract the proliferative effect of 0.1 mg/day of transdermal estradiol, a relatively high dose); and Lewis also concluded that the unusually high salivary progesterone levels constituted a "paradox" and could therefore not be used to measure progesterone absorption. In fact, they claimed that the low plasma and red blood cell progesterone levels that they observed confirmed low absorption of progesterone given topically. A review by Stanczyk (2005) discussed this controversy and confirmed that antiproliferative effects on the endometrium have been observed with progesterone cream, even when serum levels are low, and that the observed high salivary levels of progesterone arise because of rapid uptake and release of steroids by red blood cells passing through the capillaries. This quickly transports

progesterone to the salivary glands and other tissues and does not result in elevated red blood cell progesterone levels because of the speed with which the hormone is released. Therefore a low serum level cannot be used as evidence for a lack of absorption of progesterone from transdermal formulations.

There is already significant evidence that progesterone, unlike progestins, has no adverse effects on cardiovascular risk factors. No change in any of the thrombotic or inflammatory markers studied (total factor VII:C, factor VIIa, factor V, fibrinogen, antithrombin, PAI-1, CRP, TNFα and IL-6) was observed, despite significant symptomatic improvement compared to placebo, in 30 women receiving 20 mg/day progesterone cream for 4 weeks (Stephenson 2004). When progesterone (an oral micronized preparation) was used in one group in the PEPI study in place of MPA, this group had a significantly higher HDL cholesterol levels than the MPA group, indicating a different pharmacological effect than the progestin with a more favorable effect on blood lipids (Writing Group for the PEPI Trial, 1995). In fact, the authors of the WHI estrogen-progestin study pointed out in their paper (Rossouw 2002) "it remains possible that transdermal estradiol with progesterone, which more closely mimics the normal physiology and metabolism of endogenous sex hormones, may provide a different risk-benefit profile" to the one they observed. Manson (2003) reported the increased risk of cardiovascular disease with CEE/MPA in the WHI trial, noting that this was most apparent after one year of treatment. Primate studies have demonstrated a marked adverse effect of MPA on coronary artery hyperreactivity that is precisely the opposite of the protective effect seen with progesterone (Mishra 2005). In fact, progesterone tends to promote the expression of progesterone receptors in the coronary artery wall (Minshall 1998). Furthermore, MPA, but not progesterone, negated the coronary vasospasm protective effects of estradiol, shown by measuring intracellular calcium and protein kinase C signals (Miyagawa 1997b, Minshall 1998).

Progesterone, unlike synthetic progestins, has no adverse effects on cardiovascular risk factors.

Not only is there a lack of adverse effects of progesterone on the cardiovascular system, there is also evidence of beneficial effects. A progesterone vaginal gel produced an increase in exercise tolerance in postmenopausal women with coronary artery disease or previous myocardial infarction who were being treated with estradiol, while MPA did not, compared with estradiol alone (Rosano 2000), suggesting an advantage for progesterone in women at risk for cardiovascular disease. Also, transdermal progesterone treatment in oophorectomized rhesus monkeys decreased the expression of elements of the inflammatory responses, i.e., thromboxane receptors, in coronary artery muscle (Minshall 2001), and this may be the key to progesterone's long term beneficial role as shown by its ability to reduce coronary hyperreactivity via attenuation of thromboxane prostanoid receptor expression even in the presence of atherosclerosis in oophorectomized rhesus monkeys (Hermsmeyer 2004).

The benefit of reducing the risk of heart attacks, angina pectoris, stroke, and other major heart and vascular disease by restoring the hormone balance that can delay the decline in cardiovascular function for decades, represents a major conceptual breakthrough for women. Supporting the hyperreactivity hypothesis (discussed earlier in the section on Cardiovascular Disease), Koh (2004) reported that progesterone, together with lower dose CEE, had comparable beneficial effects to conventional high dose CEE on flow mediated dilation, high density lipoproteins, and triglycerides, which may suggest that peripheral vascular function in postmenopausal women is markedly improved by progesterone's direct actions on the vascular wall.

Preliminary data from an ongoing, 3-year prospective study of low-dose transdermal estradiol and progesterone cream in 150 peri- and postmenopausal women already show statistically significant favorable effects on biomarkers for cardiovascular disease risk, mood and quality of life measures in the treated group compared with controls after eight weeks of follow-up (Stephenson 2007). Baseline cardiovascular measures were similar in both groups. After eight weeks of intervention, there was no significant difference between groups in plasma fibrinogen, nitric

oxide, myeloperoxidase and plasminogen activator inhibitor levels; however, significant reductions in systolic blood pressure, fasting blood glucose, and Homeostasis Metabolic Assessment of Insulin Resistance were seen in the treated group, as well as a decrease in pulse pressure and a 20% reduction in plasma triglyceride levels in women who had levels ≥ 130 mg/dl at baseline. The treated group also reported a significant decrease in menopausal symptoms, and showed a significant improvement (decrease) in Greene Climacteric Scale, Hamilton Anxiety and Hamilton Depression scores compared to controls. Longer term and larger studies are needed to confirm these effects.

Regarding breast cancer, a large French cohort study (54,548 women, average age 52.8 years (Fournier 2005) showed that combined HT with estrogen (either oral or transdermal) and progestins carries an increased risk of breast cancer compared with estrogens plus oral micronized progesterone, the latter combination being commonly prescribed in France.

Combined HT with estrogen (either oral or transdermal) and synthetic progestogens carries a significantly increased risk of breast cancer compared with estrogens plus oral micronized progesterone.

Vitamin D

Need (2000) established that postmenopausal women should maintain 25(OH)D levels over 16 ng/ml (the lower limit of normal for healthy young people) in order to keep serum parathyroid hormone at normal levels; lower 25(OH)D levels are accompanied by a rise in parathyroid hormone, which is thought to accelerate bone loss. The recently updated NAMS guidelines for postmenopausal osteoporosis treatment recommend adequate calcium (at least 1000 mg/day) and vitamin D intake along with other lifestyle measures such as fall prevention, as first-line treatment (NAMS 2006). Since vitamin D insufficiency is one of the most common hormonal deficiencies in the postmenopausal years and has enormous implications for both bone and cardiovascular health, it is likely to be one of the simplest "hormone replacement" options available that may have the greatest impact on postmenopausal health. Dietary vitamin D supplementation with 800 to 1000 IU/day, at least twice the current recommended daily intake, is required to maintain minimum blood levels of 30 ng/ml in older women, as suggested by a review of the recommendations of several experts in the field (Dawson-Hughes 2005). This recommendation is particularly important in northern climates where the daily sunshine hours are limited, in winter time, and in black women, whose sunlight requirements are considerably greater than those of fair-skinned people for adequate vitamin D synthesis in the skin. The negligible vitamin D content of most foods and the inadequate amounts of the vitamin in over-the-counter supplements has also resulted in significant concern, particularly as cardiovascular disease rates soar (Zittermann 2006).

CONCLUSIONS

This review has attempted to refocus attention on our current conceptualization of "hormone replacement therapy." The idea of replacement presupposes that something is deficient. Menopause is a natural transition that women undergo as they age beyond the normal childbearing phase and, just like puberty or pregnancy, the body makes changes requisite with its altered status. Short-term physiologic changes accompanying the shifting hormonal patterns during perimenopause, manifesting as hot flashes and night sweats and commonly referred to as "vasomotor symptoms," are very problematic for some women and may require treatment. Also, urogenital symptoms can be the result of a combination of reduced sexual activity, as libido often wanes during this period along with a normal decline in hormone levels, and if these cause distress they, too, can be treated.

Longer term treatment of postmenopausal women with hormones in an attempt to prevent future disease is now an area of active research. The treatment of some hormonal deficiencies that have recently been identified in postmenopausal

women, such as inadequate vitamin D levels, could reap significant long term health benefits, because of the serious health implications of vitamin D deficiency, especially for cardiovascular and bone health. In addition, the health consequences of inadequate exercise, poor dietary choices, and other lifestyle factors have their own consequences for postmenopausal women, and these may all have as important an impact in the long term as do the falling levels of sex steroid hormones from ovarian decline.

Finally, it is important to understand that women are becoming more aware of solutions to their own health problems. The impact of information widely available to the public regarding hormone options is changing the face of healthcare, as women expect their providers to be informed in this rapidly changing and complex area. Clinicians continue to need results of high quality research in order to make informed recommendations to their patients. Knowledge about physiologic changes occurring in the menopause transition and effective ways to help patients traverse this time of change is expanding rapidly. Certainly more research is always needed, yet decisions must be made on a daily basis to assist patients, using the best information currently available. It is hoped that this publication will be helpful in making those decisions and recommendations.

Any errors or ommissions are those of the author

REFERENCES

Affinito P, Di Carlo C, Di Mauro P, Napolitano V, Nappi C (1994). Endometrial hyperplasia: efficacy of a new treatment with a vaginal cream containing natural micronized progesterone. Maturitas 1994; 20(2-3):191-8.

Aloia JF, Vaswani A, Yeh JK, Ross PL, Flaster E, Dilmanian FA (1994). Calcium supplementation with and without hormone replacement therapy to prevent postmenopausal bone loss. Ann Int Med 1994; 120(2):97-103.

Anasti JN, Leonetti HB, Wilson KJ (2001). Topical progesterone cream has antiproliferative effect on estrogen-stimulated endometrium. Obstet Gynecol 2001; 97(4 Suppl 1):S10.

Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S; Women's Health Initiative Steering Committee (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291(14):1701-12.

Arlt W (2006). Androgen therapy in women. Eur J Endocrinol 2006; 154:1-11.

Avis NE, Stellato R, Crawford S, Johannes C, Longcope C (2000). Is there an association between menopause status and sexual functioning? Menopause 2000; 7:297-309.

Bachmann GA, Nevadunsky NS (2000). Diagnosis and treatment of atrophic vaginitis. Am Fam Physician 2000; 61(10):3090-6.

Barrett-Connor E, Grady D, Stefanick ML (2005). The rise and fall of menopausal hormone therapy. Ann Rev Public Health 2005; 26:115-40.

Baulieu E-E, Thomas G, Legrain S, Lahlou N, Roger M, Debuire B, Faucounau V, Girard L, Hervy M-P, Latour F, Leaud M-C, Mokrane A, Pitti-Ferrandi H, Trivalle C, de Lacharriere O, Nouveau S, Rakoto-Arison B, Souberbielle J-C, Raison J, Le Bouc Y, Raynaud A, Girerd X, Forette F (2000). Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge study to a sociobiomedical issue. Proc Natl Acad Sci 2000; 97(8):4279-84.

Binkley N, Krueger D (2005). Combination therapy for osteoporosis: considerations and controversy. Curr Osteoporos Rep 2005; 3(4):150-4.

Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B (2005). Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005; 293(18):2257-64.

Bygdeman M, Swahn ML (1996). Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. Maturitas 1996; 23(3):259-63.

Casanas-Roux F, Nisolle M, Marbaix E, Smets M, Bassil S, Donnez J (1996). Morphometric, immunohistological and three-dimensional evaluation of the endometrium of menopausal women treated by oestrogen and Crinone, a new slow-release vaginal progesterone. Human Reprod 1996; 11(2):357-63.

Centers for Disease Control and Prevention (2001-3 data). National Center for Health Statistics. Health Data for All Ages. http://www.cdc.gov/nchs/health_data_for_all_ages.htm [accessed 6/28/06].

Chang KJ, Lee TT, Linares-Cruz G, Fournier S, de Lignieres B (1995). Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertil Steril 1995; 63(4):785-91.

Chen WY, Manson JE, Hankinson SE, Rosner B, Holmes MD, Willett WC, Colditz GA (2006). Unopposed estrogen therapy and the risk of invasive breast cancer. Arch Intern Med. 2006; 166(9):1027-32.

Cicinelli E, de Ziegler D, Galantino P, Pinto V, Barba B, Morgese S, Schonauer S (2002). Twice-weekly transdermal estradiol and vaginal progesterone as continuous combined hormone replacement therapy in postmenopausal women: a 1-year prospective study. Am J Obstet Gynecol 2002; 187(3):556-60.

Colditz GA (1998). Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. J Natl Cancer Inst 1998; 90(11):814-23.

Cowan LD, Gordis L, Tonascia JA, Jones GS (1981). Breast cancer incidence in women with a history of progesterone deficiency. Am J Epidemiol 1981; 114(2):209-17.

Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R (2005). Estimates of optimal vitamin D status. Osteoporos Int. 2005;16(7):713-6.

Davila GW, Singh A, Karapanagiotou I, Woodhouse S, Huber K, Zimberg S, Seiler J, Kopka SL (2003). Are women with urogenital atrophy symptomatic? Am J Obstet Gynecol 2003; 188(2):382-8.

Dennerstein L, Hayes RD (2005). Confronting the challenges: epidemiological study of female sexual dysfunction and the menopause. J Sex Med 2005; 2(Suppl 3):118-32.

Dennerstein L, Lehert P, Burger H (2005). The relative effects of hormones and relationship factors on sexual function of women through the natural menopausal transition. Fertil Steril 2005; 84(1):174-80.

Dennerstein L, Koochaki P, Barton I, Graziottin A (2006). Hypoactive sexual desire disorder in menopausal women: a survey of Western European women. J Sex Med 2006; 3(2):212-22.

Dören M, Nilsson J-A, Johnell O (2003). Effects of specific post-menopausal hormone therapies on bone mineral density in post-menopausal women: a meta-analysis. Human Reprod 2003; 18(8):1737-1746.

Ettinger B (2004). Rationale for use of lower estrogen doses for post-menopausal hormone therapy. Business Briefing: Women's Healthcare 2004; 1-6. http://www.touchbriefings.com/pdf/992/Ettinger_pap.pdf [accessed 6/27/06].

Ferrero S, Gerbaldo D, Fulcheri E, Cristoforoni P (2002). Vaginal micronized progesterone in continuous hormone replacement therapy. A prospective randomized study. Minerva Ginecol 2002; 54(6):519-30.

Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F (2005). Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer 2005; 114(3):448-54.

Freeman EW, Sammel MD, Lin H, Gracia CR, Kapoor S, Ferdousi T (2005). The role of anxiety and hormonal changes in menopausal hot flashes. Menopause 2005; 12(3):258-66.

Ganti AK, Sahmoun AE, Panwalkar AW, Tendulkar KK, Potti A (2006). Hormone replacement therapy is associated with decreased survival in women with lung cancer. J Clin Oncol 2006; 24(1):59-63.

Gass M, Dawson-Hughes B (2006). Preventing osteoporosis-related fractures: an overview. Am J Med 2006; 119(4 Suppl 1):S3-S11.

Gracia CR, Freeman EW (2004). Acute consequences of the menopausal transition: the rise of common menopausal symptoms. Endocrinol Metab Clin North Am 2004; 33(4):675-89.

Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, Ernster VL, Cummings SR (1992). Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med. 1992 Dec 15;117(12):1016-37.

Greendale GA, Espeland M, Slone S, Marcus R, Barrett-Connor E, PEPI Safety Follow-up Study (PSFS) Investigators (2002). Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. Arch Intern Med 2002; 162(6):665-72.

Hale GE, Hitchcock CL, Williams LA, Vigna YM, Prior JC (2003). Cyclicity of breast tenderness and night-time vasomotor symptoms in mid-life women: information collected using the Daily Menopause Diary. Climacteric 2003; 6(2):128-39.

Hayes R, Dennerstein L (2005). The impact of aging on sexual function and sexual dysfunction in women: a review of population-based studies. J Sex Med 2005; 2(3):317-30.

Hemminki E, McPherson K (1997). Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. BMJ 1997; 315(7101):149-53.

Hermann AC, Nafziger AN, Victory J, Kulawy R, Rocci ML Jr, Bertino JS Jr (2005). Over-the-counter progesterone cream produces significant drug exposure compared to a food and drug administration-approved oral progesterone product. J Clin Pharmacol 2005; 5(6):614-9.

Hermsmeyer RK, Mishra RG, Pavcnik D, Uchida B, Axthelm MK, Stanczyk FZ, Burry KA, Illingworth DR, Kaski JC, Nordt FJ (2004). Prevention of coronary hyperreactivity in pre-atherogenic menopausal rhesus monkeys by transdermal progesterone. Arteriosclerosis Thromb Vasc Biol 2004; 24:955-961.

Holick MF (2005a). Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. South Med J 2005; 98(10):1024-1027.

Holick MF (2005b). The vitamin D epidemic and its health consequences. J Nutr 2005; 135(11):2739S-48S.

Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, Petruschke RA, Chen E, de Papp AE (2005). Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab. 2005; 90(6):3215-24.

Holick MF (2006). High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006; 81(3):353-73.

Holzer G, Riegler E, Honigsmann H, Farokhnia S, Schmidt JB (2005). Effects and side-effects of 2% progesterone cream on the skin of peri- and postmenopausal women: results from a double-blind, vehicle-controlled, randomized study. Br J Dermatol 2005; 153(3):626-34.

Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E (1998). Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280(7):605-13.

Ishibashi H, Suzuki T, Suzuki S, Niikawa H, Lu L, Miki Y, Moriya T, Hayashi S, Handa M, Kondo T, Sasano H (2005). Progesterone receptor in non-small cell lung cancer – a potent prognostic factor and possible target for endocrine therapy. Cancer Res 2005; 65(14):6450-8.

Johnson BD, Shaw LJ, Buchthal SD, Merz CNB, Kim H-W, Scott KN, Doyle M, Olson MB, Pepine CJ, den Hollander J, Sharaf B, Rogers WJ, Mankad S, Forder JR, Kelsey SF, Pohost GM (2004). Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease results from the National Institutes of Health–National Heart, Lung, and Blood Institute–Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004; 109:2993-2999.

Key T, Appleby P, Barnes I, Reeves G, Endogenous Hormones and Breast Cancer Collaborative Group (2002). Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002; 94(8):606-16.

Koh KK, Shin M-S, Sakuma I, Ahn JY, Jin DK, Kim HS, Kim DS, Han SH, Chung W-J, Shin EK (2004). Effects of conventional or lower doses of hormone replacement therapy in postmenopausal women. Arterioscler Thromb Vasc Biol. 2004; 24:1516-1521.

Kreiger N, Sloan M, Cotterchio M, Kirsh V (1999). The risk of breast cancer following reproductive surgery. Eur J Cancer 1999; 35(1):97-101.

Laan E, van Lunsen RH (1997). Hormones and sexuality in postmenopausal women: a psychophysiological study. J Psychosom Obstet Gynaecol 1997; 18(2):126-33.

Labrie F, Luu-The V, Bélanger A, Lin S-X, Simard J, Pelletier G (2005). Is dehydroepiandrosterone a hormone? J Endocrinol 2005; 187:169-96.

Lee JR (1994). Successful menopausal osteoporosis treatment restoring osteoclast/osteoblast equilibrium. Townsend Letter for Doctors and Patients 1994; 133/134:900-905.

Lee JR, Hopkins V (2004). What your doctor may not tell you about menopause: the breakthrough book on natural hormone balance. Revised Edition 2004. Warner Books, New York, NY.

Leiblum S, Bachmann G, Kemmann E, Colburn D, Swartzman L (1983). Vaginal atrophy in the postmenopausal woman. The importance of sexual activity and hormones. JAMA 1983; 249(16):2195-8.

Leonetti HB, Longo S, Anasti JN (1999). Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. Obstet Gynecol 1999; 94(2):225-8

Leonetti HB, Anasti JN, Landes J (2003a). Topical progesterone cream: an alternative progestin in hormone therapy. Obstet Gynecol 2003; 101(4 Suppl):85.

Leonetti HB, Wilson KJ, Anasti JN (2003b). Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium. Fertil Steril 2003; 79(1):221-2.

Leonetti HB, Landes J, Steinberg D, Anasti JN, (2005). Topical progesterone cream as an alternative progestin in hormone therapy. Altern Ther Health Med 2005; 11(6):36-38.

Lewis JG, McGill H, Patton VM, Elder PA (2002). Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women. Maturitas 2002; 41(1):1-6.

Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH (2002). Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. JAMA 2002; 287(20):2668-76.

Manolagas SC, Kousteni S, Jilka RL (2002). Sex steroids and bone. Recent Prog Horm Res 2002; 57:385-409.

Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M; Women's Health Initiative Investigators (2003). Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349(6):523-34.

Miller KK (2001). Androgen deficiency in women. J Clin Endocrinol Metab 2001; 86(6):2395-2401.

Miller VM, Clarkson TB, Harman SM, Brinton EA, Cedars M, Lobo R, Manson JE, Merriam GR, Naftolin F, Santoro N (2005). Women, hormones, and clinical trials: a beginning, not an end. J Appl Physiol 2005; 99:381-3.

Minshall RD, Stanczyk FZ, Miyagawa K, Uchida B, Axthelm M, Novy M, Hermsmeyer K (1998). Ovarian steroid protection against coronary artery hyperreactivity in rhesus monkeys. J Clin Endocrinol Metab 1998; 83(2):649-59.

Minshall RD, Pavcnik D, Halushka PV, Hermsmeyer K (2001). Progesterone regulation of vascular thromboxane A2 receptors in rhesus monkeys. Am J Physiol Heart Circ Physiol 2001; 281:H1498–H1507.

Mishra RG, Hermsmeyer RK, Miyagawa K, Sarrel P, Uchida B, Stanczyk FZ, Burry KA, Illingworth DR, Nordt FJ (2005). Medroxyprogesterone acetate and dihydrotestosterone induce coronary hyperreactivity in intact male rhesus monkeys. J Clin Endocrinol Metab 2005; 90: 3706–3714.

Missmer SA, Eliassen AH, Barbieri RL, Hankinson SE (2004). Endogenous estrogen, androgen, and progesterone concentrations and breast cancer risk among postmenopausal women. J Natl Cancer Inst 2004; 96(24):1856-65.

Miyagawa K, Rösch J, Stanczyk F, Hermsmeyer K (1997a). Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. Nature Med 1997; 3(3):324-7.

Miyagawa K, Vidgoff J, Hermsmeyer K (1997b). Ca2+ release mechanism of primate drug-induced coronary vasospasm. Am J Physiol 1997; 272(41):H2645-H2654.

Mohr PE, Wang DY, Gregory WM, Richards MA, Fentiman IS (1996). Serum progesterone and prognosis in operable breast cancer. Br J Cancer 1996; 73(12):1552-5.

Montz FJ, Bristow RE, Bovicelli A, Tomacruz R, Kurman RJ (2002). Intrauterine progesterone treatment of early endometrial cancer. Am J Obstet Gynecol 2002; 186(4):651-7.

Moore C, Murphy MM, Keast DR, Holick MF (2004). Vitamin D intake in the United States. J Am Diet Assoc 2004; 104(6):980-3.

Morali G, Polatti F, Metelitsa EN, Mascarucci P, Magnani P, Marre GB (2006). Open, non-controlled clinical studies to assess the efficacy and safety of a medical device in form of gel topically and intravaginally used in postmenopausal women with genital atrophy. Arzneimittelforschung 2006; 56(3):230-8.

Nachtigall LE (1994). Comparative study: Replens versus local estrogen in menopausal women. Fertil Steril 1994; 61(1):178-80.

National Institutes of Health (2005). National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. Ann Intern Med 2005; 142(12 Pt 1):1003-13.

Nawroth P, Pirzer R, Fohr B, Schilling T, Ziegler R, Bierhaus A, Kasperk C (2003). [Osteoporosis and cardiovascular disease – two sides of the same coin?] Med Klin (Munich) 2003; 98(8):437-46.

Need AG, Morris HA, Horowitz M, Nordin C (1993). Effects of skin thickness, age, body fat, and sunlight on serum 25-hydroxyvitamin D. Am J Clin Nutr. 1993; 58(6):882-5.

Need AG, Horowitz M, Morris HA, Nordin BC (2000). Vitamin D status: effects on parathyroid hormone and 1, 25-dihydroxyvitamin D in postmenopausal women. Am J Clin Nutr. 2000; 71(6):1577-81.

Need AG, O'Loughlin PD, Morris HA, Horowitz M, Nordin BE (2004). The effects of age and other variables on serum parathyroid hormone in postmenopausal women attending an osteoporosis center. J Clin Endocrinol Metab 2004; 89(4):1646-9.

Neergaard L (2006). New lung cancer studies examine effect of estrogen. Seattle Times, May 30th 2006.

Nelson HD, Haney E, Humphrey L, Miller J, Nedrow A, Nicolaidis C, Vesco K, Walker M, Bougatsos C, Nygren P (2005). Management of menopause-related symptoms. Evidence Report/Technology Assessment No. 120. (Prepared by the Oregon Evidence-Based Practice Center, under Contract No. 290-02-0024.) AHRQ Publication No. 05-E016-2. Rockville, MD: Agency for healthcare Research and Quality. March 2005. Full text at: http://www.ahrq.gov/downloads/pub/evidence/pdf/menopause/menopaus.pdf [accessed 6/14/06].

Norman PE, Powell JT (2005). Vitamin D, shedding light on the development of disease in peripheral arteries. Arterioscler Thromb Vasc Biol 2005; 25:39-46.

North American Menopause Society (2004). Treatment of menopause-associated vasomotor symptoms: position statement of the North American Menopause Society. Menopause 2004; 11(1):11-33.

North American Menopause Society (2006). Position statement. Management of osteoporosis in postmenopausal women: 2006 position statement of the North American Menopause Society. Menopause 2006; 13:340-367.

O'Leary P, Feddema P, Chan K, Taranto M, Smith M, Evans S (2000). Salivary, but not serum or urinary levels of progesterone are elevated after topical application of progesterone cream to pre- and postmenopausal women. Clin Endocrinol (Oxf) 2000; 53(5):615-20.

Ouyang P, Michos ED, Karas RH (2006). Hormone replacement therapy and the cardiovascular system: lessons learned and unanswered questions. J Am Coll Cardiol 2006; 49(9):1741-53.

Parsons A, Merritt D, Rosen A, Heath H, Siddhanti S, Plouffe L (2003). Effect of raloxifene on the response to conjugated estrogen vaginal cream or nonhormonal moisturizers in postmenopausal vaginal atrophy. Obstet Gynecol 2003; 101(2):346-52.

Peterlik M, Cross HS (2005). Vitamin D and calcium deficits predispose for multiple chronic diseases. Eur J Clin Invest 2005; 35(5):290-304.

Poole KE, Loveridge N, Barker PJ, Halsall DJ, Rose C, Reeve J, Warburton EA (2006). Reduced vitamin D in acute stroke. Stroke 2006; 37(1):243-5.

Prestwood KM (2003). Editorial: The Search for Alternative Therapies for Menopausal Women: Estrogenic Effects of Herbs. J Clin Endocrinol Metab 2003; 88(9):4075-4076.

Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M (2003). Ultralow-dose micronized 17αestradiol and bone density and bone metabolism in older women: a randomized controlled trial. JAMA 2003; 290(8):1042-1048.

Prior JC (1990). Progesterone as a bone-trophic hormone. Endocr Rev 1990; 11(2):386-98.

Prior JC, Vigna YM, Schechter MT, Burgess AE (1990). Spinal bone loss and ovulatory disturbances. N Engl J Med 1990; 323(18):1221-7.

Prior JC, Vigna YM, Barr SI, Rexworthy C, Lentle BC (1994). Cyclic medroxyprogesterone treatment increases bone density: a controlled trial in active women with menstrual cycle disturbances. Am J Med 1994; 96(6):521-30.

Prior JC, Vigna YM, Wark JD, Eyre DR, Lentle BC, Li DK, Ebeling PR, Atley L (1997). Premenopausal ovariectomy-related bone loss: a randomized, double-blind, one-year trial of conjugated estrogen or medroxyprogesterone acetate. J Bone Miner Res 1997; 12(11):1851-63.

Prior JC (1998). Perimenopause: the complex endocrinology of the menopausal transition. Endocrine Rev 1998; 19(4): 397-428.

Prior JC (2006a). Estrogen deficiency: the wrong idea about menopause. http://www.cemcor.ubc.ca/articles/misc/estrogen_deficiency_wrong.shtml [accessed 5/27/2006].

Prior JC (2006b). Letter from Dr. Kailey Madrona to Dr. Mark Aster. In: "Estrogen's Storm Season: Stories of Perimenopause" by J.C. Prior, Center for Menstrual Cycle and Ovulation Research (CeMCOR), 2006, pp. 214-220.

Rizzoli R, Eisman J, Ljunggren O, Chandler J, Norquist J, Krishnarajah G, Lim S (2006). Abstract P283: Risk factors for vitamin D inadequacy among women with osteoporosis: an international study. Presented at the 33rd European Symposium on Calcified Tissues, 10-14th May 2006, Prague, Czech Republic.

Rosano GM, Webb CM, Chierchia S, Morgani GL, Gabraele M, Sarrel PM, de Ziegler D, Collins P (2000). Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women, J Am Coll Cardiol 2000; 36(7):2154-9.

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J, Writing Group for the Women's Health Initiative Investigators (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002; 288(3):321-33.

Sato Y, Kaji M, Metoki N, Satoh K, Iwamoto J (2003). Does compensatory hyperparathyroidism predispose to ischemic stroke? Neurology 2003; 60(4):626-9.

Schneider DL (2006). The effect of vitamin D on bone and neuromuscular function. Presented at the symposium "Treatment paradigms, challenging concepts: examining biomechanics and hip structure analysis", San Diego, CA, February 2nd 2006. http://www.medscape.com/viewprogram/5368 [accessed 6/26/06].

Siegfried JM (2006). Hormone replacement therapy and decreased lung cancer survival. J Clin Oncol 2006; 24(1):9-10.

Society of Obstetricians and Gynaecologists of Canada (2005). SOGC clinical practice guidelines. The detection and management of vaginal atrophy. Number 145, May 2004. Int J Gynaecol Obstet 2005; 88(2):222-8.

Somjen D, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, Jaccard N, Knoll E, Stern N (2005). 25-Hydroxyvitamin D3-1αhydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation 2005; 111:1666-71.

Sowers M, Randolph JF Jr, Crutchfield M, Jannausch ML, Shapiro B, Zhang B, La Pietra M (1998). Urinary ovarian and gonadotropin hormone levels in premenopausal women with low bone mass. J Bone Miner Res 1998; 13(7):1191-202.

Stanczyk FZ (2003). All progestins are not created equal. Steroids 2003; 68:879-90.

Stanczyk FZ, Paulson RJ, Roy S (2005). Percutaneous administration of progesterone: blood levels and endometrial protection. Menopause 2005; 12(2):232-7.

Stefanick ML, Cochrane BB, Hsia J, Barad DH, Liu JH, Johnson SR (2003). The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. Ann Epidemiol. 2003; 13(9 Suppl):S78-86.

Stefanick ML (2005). Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. Am J Med 2005; 118(128): 64S-73S.

Stephenson K, Price C, Neuenschwander P, Kurdowska A, Pinson B, Stephenson D, Stephenson J, Zava D, Alfred D, Krupa A, Mahoney D, Bevan M (2004). Topical progesterone cream does not increase thrombotic and inflammatory factors in postmenopausal women. Blood 2004; 104(11):414b-415b.

Stephenson K, Kurdowska A, Neuenschwander P, Loewenstein I, Olusola P, Pinson B, Stephenson D, Kinsey R, Stephenson J, Stephenson J, Kapur S, Zava D (2007). Transdermal estradiol and progesterone improve mood indicators, quality of life, and biomarkers of cardiovascular disease in perimenopausal and postmenopausal women. Abstracts from the 47th Annual Conference on Cardiovascular Disease Epidemiology & Prevention, Orlando, Feb 28 – Mar 3 2007. Circulation 2007; 115(8) Abstract.

van der Laak JA, de Bie LM, de Leeuw H, de Wilde PC, Hanselaar AG (2002). The effect of Replens on vaginal cytology in the treatment of postmenopausal atrophy: cytomorphology versus computerised cytometry. J Clin Pathol 2002; 55(6):446-51.

Vashisht A, Wadsworth F, Carey A, Carey B, Studd J (2005). Bleeding profiles and effects on the endometrium for women using a novel combination of transdermal estradiol and natural progesterone cream as part of a continuous combined hormone replacement regimen. BJOG 2005; 112(10):1402-6.

Woo SB, Hellstein JW, Kalmar JR (2006). Systematic review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006; 144(10):753-61.

Wren BG, McFarland K, Edwards L, O'Shea P, Sufi S, Gross B, Eden JA (2000). Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women. Climacteric 2000; 3(3):155-60.

Wren BG, Champion SM, Willetts K, Manga RZ, Eden JA (2003). Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. Menopause 2003; 10(1):13-18.

Writing Group for the PEPI Trial (1995). Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA 1995; 273(3):199-208.

Writing Group for the PEPI Trial (1996). Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA 1996; 276(17):1389-96.

Zittermann A (2003). Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr 2003; 89(5):552-72.

Zittermann A, Scheithoff SS, Koerfer R (2005). Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr 2005; 94(4):483-92.

Zittermann A (2006). Vitamin D and disease prevention with special reference to cardiovascular disease. Prog Biophys Mol Biol 2006; 92(1):39-48.

www.womeninbalance.org