THE STANDARD

Volume 4, No.1 2001

A CONCISE UPDATE OF IMPORTANT ISSUES CONCERNING NATURAL HEALTH INGREDIENTS

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MENOPAUSE - A Natural Transition

Over 40 million women are currently post-menopausal in the United States. The fact that those numbers will increase to 60 million in the next 10 years and the attitudes about menopause are continuing to move from being viewed as a clinical syndrome to a natural transition have opened the way for more natural and comprehensive management of menopausal symptoms. This review will discuss the physiological and clinical aspects of menopause, with a view to both the inevitable and preventable consequences of the climacteric transition. We will focus on the primary menopausal symptoms (hot flushes, insomnia etc.) as well as the secondary conditions (osteoporosis, heart disease etc.) associated with post-menopausal hormone levels. A brief discussion of conventional therapies will be followed by a review of natural alternatives and preventative measures. It will be clear that the treatment of menopausal symptoms can be as natural as the transition itself.

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Somewhere between the ages of 45 and 55, most women experience a change in their normal menstrual cycle that results in a complete cessation of the cycle. Those transitional years, often referred to as the perimenopausal or climacteric years, lead to a number of physiological and emotional changes that affect a woman's quality of life. However, while the menopausal transition is experienced by women around world, the unique combination of diet, lifestyle (particularly stress), cultural attitudes and longevity give it particularly prominence in the Western world. The additional fact that menopause is accompanied by increased incidence of bone fractures, heart disease, depression, fatigue, loss in mental acuity, increased sexual difficulties and various cancers has often lead to the conclusion that the transition itself must be an unnatural state, or even a diseased state. A correct perception of this natural transition, along with the use of natural dietary and supplemental protocols, may completely alter the quality of life of the growing number of women entering this phase of their lives.

Menopause physiology

The female hormonal cycle is an exquisitely controlled system that includes the hypothalamus, pituitary, adrenal, thyroid and gonadal tissues; involving both positive and negative feedback loops. We will use a future review to discuss the intricate nature of the menstrual cycle, and only discuss

In My Opinion

What is a disease? Sounds too simple to be a question worth pondering, but when does a set of symptoms leave the range of normal variance and enter into abnormal, unhealthy…disease. Menopause is a classic example. As a function of aging, it is considered inevitable; but some women experience symptoms severe enough to desire pharmacological treatment lasting decades. Others experience no symptoms at all. Is it a disease for some, and not for others? Other conditions, like fatigue, aging, male pattern baldness, general aches and pains, poor digestion, decreased memory, menstrual irregularities and decrease in libido are some of the many conditions that may fall into the same category.

This question is made even more difficult when considering the role of FDA in determining what claims can be made of supplement products. For instance, the following claim is allowable, "This product helps support healthy bones", while this claim is not, "This product helps support healthy bones in aging women". The difference is the implication of menopause with the associated risk factor of osteoporosis (a disease), which is a drug claim requiring FDA drug approval. But who defines what is to become a disease, and who benefits.

Again, menopause can be used as an example. The isolation of conjugated estrogens and synthetic hormone derivatives are difficult for pharmaceutical firms to sell unless menopause is a disease. Often a drug campaign is focused as much on promoting the disease as it is the drug itself. Is it any wonder that awareness and diagnosis of ADHD exploded when Ritalin became available. One could almost say that Ritalin has defined a disorder that may not even have existed until the "cure" was discovered. The drug companies only have an advantage when they can convince both the FDA and the public that these are diseases and therefore require pharmaceuticals for their treatment. Millions of American children are now being treated with what they are led to believe is a Ritalin-deficiency disease. Likewise, pharmaceutical companies would like menopause to be defined simply as an estrogen-deficiency disease, because the "cure" is already available.

We are at a vital time in defining what will define a disease, and what will differentiate a drug claim and a health claim. There need to be regulations that allow the approval of truthful claims for any substance that is proven safe and effective. If the compound is a natural substance (without patent protection) the threshold for making these claims should be such that those substances meeting a standard criteria (eg. a monograph) shall be able to make truthful claims, irrespective of disease implications. This is the only way to increase the safety and efficacy of dietary supplements without allowing the whole industry to be swallowed by the pharmaceutical giants. As long as we allow them to define what constitutes a disease, and allow major media outlets to pipeline their campaign of supplement dangers and ineffectiveness; the possibility of our demise remains close at hand.

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the results of its gradual ceasing here (although surgical menopause, a result of removing the uterus or ovaries, may have similar treatments).

At birth, each woman is endowed with 1-2 million primordial follicles. This pool of follicles decreases to about 300,000 by the time of menarche (puberty). Each menstrual cycle, follicle stimulating hormone recruits several hundred to several thousand follicles. Of these, only one (or sometimes several) mature to the point of ovulation while all the others die by atresia. This process results in approximately 400 or so ovulatory cycles within a women's lifetime and constitutes what is normally referred to as the premenopausal or reproductive years.

The number of follicles left in the ovary reserve seems to be critical to the regulation of the cycle. At about 38 years of age, when approximately 25,000 follicles remain, the rate at which follicles are recruited increases nearly two-fold, resulting in a rapid decrease in the ovary reserve. Follicle stimulating hormone (FSH) levels in these women increases throughout the cycle, signaling the beginning of a loss in the feedback mechanisms. Many researchers believe that the rise in FSH is related to the decreased ovarian production of molecules called inhibins, which are believed to inhibit pituitary production of FSH. Few women notice any dramatic changes at this time since estradiol (E2) and progesterone levels are affected little by these changes (although fecundity is significantly reduced at this age).

By age 51, the median age for the final menstrual period, the ovary reserve is about 1000. This is typically when the "symptoms" of menopause occur, as it corresponds with a significant drop in estrogen production (usually beginning 6 months to one year before the final menstrual period). It is significant to note that while a woman may stop menstruating at this time, endogenous cycling and ovulation may still occur for months and even years. This is important to understand because treatment of endogenously cycling "post" menopausal women can differ from truly post-menopausal protocols.

The associated symptoms and risks

Menopause would be only a curious endocrinology topic except for the fact that a number of vasomotor symptoms and major medical risk factors are associated with the reduction in estrogen production. Let us briefly review some of the most common vasomotor symptoms: hot flashes, night sweats, insomnia and genitourinary changes.

Vasomotor

Of all the signals that tell of the arrival of menopause, the hot flash (or flush) is probably the most universal. Of American menopausal women, 75% experience hot flash episodes for an average of 4 years, although only 15% experience severe episodes. The experience is a sensation of heat, sweating, flushing, chills lasting from 1 to 5 minutes. For many, anxiety and palpitations are also experienced during these hot flash episodes. A slight increase in core temperature with a dramatic increase in peripheral blood flow results in a rapid rise in skin temperature (0.5° C). Little is known about the exact physiological causes of hot flashes, although warm room temperatures (or warm compresses) can be used to induce episodes. The exact relationship of

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estrogen to hot flashes is unclear, because while estrogen replacement therapy can reduce hot flash frequencies, there is not a clear relationship between hot flash episodes and serum estrogen levels (comparing symptomatic and asymptomatic menopausal women).

The combination of hot flashes, estrogen-related altered circadian rhythms, and increased frequency of depression tends to reduce sleep quality in many women during the climacteric. While it is difficult to assess how much each factor plays in decreasing sleep quality, this is a major factor in reducing the quality of life during the menopausal transition. Often, insomnia will be the primary reason for seeking medical attention.

Genitourinary changes

Decreased estrogen during and after menopause causes physiological changes in the genital tissues. The vaginal area becomes dry, thin and loses tone as more time passes with lowered estrogen levels. Decreased lubrication and thinning of the vaginal tissues increases infections, irritations and the chance for mechanical injury. Increased urinary tract infections and incontinence are also related to a lack of tone in the tissue surrounding the bladder and urethra. These conditions, along with menopausal drops in estrogen, progesterone and testosterone can lead to a dramatic decrease in libido. Very often, treatment via hormone replacement therapy or natural remedies that address vasomotor symptoms will also improve symptoms related to the genitourinary system.

Menopausal Risk Factors

While vasomotor symptoms may be the telltale signs of menopause, they are rarely life threatening and slowly fade once a women is past the climacteric years. The permanent change in hormone levels has been implicated as a factor in the increased risk of several serious life-threatening diseases such as osteoporosis, heart disease, and cancers of the breast and endometrium. One complication with data implicating the role that menopause plays in these disease is the confounding factor that age plays. This is particularly true in the case of cardiovascular diseases, depression, decreases in cognitive ability and the decline in libido. Because, while it is true that there is an increase of each of these with menopause, men of similar ages have a dramatic increased risk of these or similar diseases, demonstrating that these factors are closely linked with aging. Let us look briefly at these conditions and their relationship to menopause.

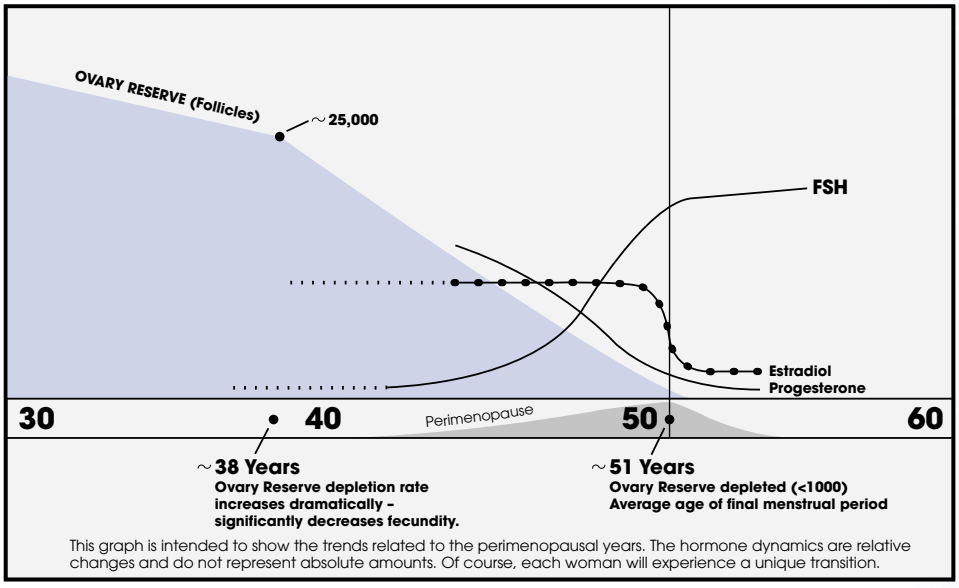
Osteoporosis

Of all the conditions mentioned, the link between estrogen depletion and osteoporosis seems to be the closest, although even this has been questioned since the loss in bone density begins well before the drop in estrogen. Osteoporosis is a metabolic bone disease that results in deterioration of the micro-architecture of the bone resulting in lower bone mass and increased risk of fractures. Nearly half of the women over 65 will experience an osteoporosis related fracture in their lifetime. These fractures (mostly of the spine, hip or forearm) dramatically increase the rate of mortality and need for long-term care. We will use a future review to discuss the complete natural approach to managing osteoporosis, but let us sketch out a few important things to remember.

One of the most critical factors in the prevention of osteoporosis is reaching peak bone mass prior to menopause. Most women do not accomplish this for a number of reasons, among them are poor diet and lack of weight bearing exercises. Several reports have shown that something as simple as the consumption of phosphoric acid in soft drinks reduces bone mineralization in postmenopausal women (1). The very low phytoestrogen intake in western diets may also play a role in this as well (see phytoestrogen insert). We do know that estrogen plays an important role in maintaining bone mass in the female by suppressing remodeling and maintaining a balance between osteoblast and osteoclast activities. As menopause is a low estrogen state, the balance is shifted toward the osteoclast (resorption) and away from osteoblast (bone building) activities. While hormone replacement therapy (HRT) is the conventional treatment for osteoporosis, bone loss resumes when HRT is stopped. For many, there exists a need to find an alternative approach that will become part of their lifestyle regimen for the 20 or 30 years they will spend after menopause.

Adequate intakes of calcium, magnesium, and trace minerals such as boron, silica, selenium, manganese and molybdenum are all important to proper bone metabolism. The mineral strontium has become a promising mineral in the treatment of osteoporosis. The hormone-like activities of vitamin D and K are also vital components in the maintenance of bone

The Dynamics of Perimenopause



This graph is intended to show the trends related to the perimenopausal years. The hormone dynamics are relative changes and do not represent absolute amounts. Of course, each woman will experience a unique transition.

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mass. Finding all the necessary components in both dietary and supplemental forms, and in a protocol that maximizes convenience and compliance is the key to ensuring a successful therapy. Again, a complete review will be forthcoming to discuss the latest research on these and other natural substances and their relation to treating osteoporosis.

Heart Disease

It has been hypothesized that menopause is associated with an increased risk of cardiovascular events, and the increase is caused by decreasing estrogen production. However, whether menopause can be concluded to be an independent risk factor is an area of controversy. The difficulty comes with the slow onset of cardiovascular deterioration and the background effects of aging. The positive correlation is related to the dramatic increase in risk when comparing pre and postmenopausal women and the reduction of risk associated with hormone replacement therapy (HRT). Long-term studies are now being conducted to determine the role estrogen, and HRT play in preventing cardiovascular related outcomes like atherosclerosis, heart attacks, stroke, and LDL cholesterol.

Factors to Consider

There are many factors that play a role in age of onset or the severity of the symptoms associated with the menopause. Studies have shown that women who experience prevalent symptoms related to premenstrual syndrome (PMS) or whose mother experienced severe vasomotor symptoms upon the climacteric have an increased prevalence of experiencing vasomotor symptoms during their menopause. These results may be due to a consistent pattern of hormone regulation through out ones life (and even genetically related) or may be a function of increased scrutiny and awareness of these symptoms.

Two extraovarian sources of estrogen exist that allow for buffering the dramatic loss at the climacteric. The adipose tissues are capable of producing estrone and this is thought to play a role in reducing some vasomotor symptoms in heavier women. While no direct relationship between body mass index (BMI) and hot flashes (or other symptoms) can be predicted in each case, in many individuals the amount of adipose tissue may relate inversely to menopausal symptoms. The other buffering source is the adrenal gland. The role of the adrenal glands and their ability to modulate stress is often not taken into consideration by doctors when treating patients with climacteric complaints. The role of the adrenal gland, as it relates to stress or menopause is beyond what can be covered in this review, although a previous article was dedicated to measuring and treating adrenal stress (*The Standard*, Vol. 3 No. 1). Suffice to say that if the adrenal gland is incapable of responding adequately to stresses put on it, the symptoms of menopause are likely to be exacerbated. Checking adrenal stress (via cortisol and DHEA-S levels) is a simple addition to many of the salivary tests that can be done to measure estradiol and progesterone. Treating an exhausted adrenal system may dramatically improve symptoms with little other intervention. Other factors to consider are social status, parity, education, smoking, exercise, hysterectomies (with or without ovarectomies), age at menarche, ethnicity, oral contraception use and occupation; all of which can play a role in the onset or severity of menopausal symptoms (54,55,56).

FACTORS THAT MAY AFFECT THE ONSET OF MENOPAUSE

EARLIER ONSET

- Removal of uterus or ovaries
- Cycle length shorter than 26 days
- Smoking or second-hand smoke (reversible)
- Lower number of full-term pregnancies
- Pelvic irradiation or chemotherapy
- Low socio-economic status
- Single marital status
- African-American or Latin descent
- Malnourishment
- Vegetarian diet
- Mother with early menopause
- History of depression

DELAYED ONSET

- Cycle length greater than 33 days
- Increased full-term pregnancies (parity)
- Use of oral contraceptives
- Moderate consumption of alcohol
- Increased consumption of phytoestrogens
- Increased Body Fat or BMI

Hormone Replacement Therapy (HRT)

Conjugated estrogens, which are a mixture of active estrogens derived from the urine of pregnant mares, have been in use in the United States since the early 1940's. The use of estrogens increased for decades following, for conditions like osteoporosis and vasomotor symptoms. In the early 1970's, after evidence strongly linked unopposed estrogen therapy (estrogens without additional progesterone) with increased risk of endometrial cancers, the long-term safety of hormone replacement therapy came into question. Until 1992, Premarin was the only FDA approved oral estrogen product, others have since been approved. Several estrogen and estrogen-progestin products are now used for the treatment of vasomotor complaints and for risk reduction of heart disease and osteoporosis.

The role of estrogens has been broadened by the use of selective estrogen receptor modulators (SERMs). These are agents that produce estrogen-like effects on some tissues (like bone) and antagonize estrogen in others

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(reproductive tissues). Tamoxifen and raloxifene are the best-studied and most used SERMs for osteoporosis and breast cancer protection.

The assumption often made is that every menopausal woman needs some form of hormone replacement therapy and should be on it indefinitely. This assumption is being challenged both for its own inherent risks and the desire of women to choose alternative and more natural routes of menopausal treatments. We have known that unopposed estrogen therapy increases the incidence of endometrial cancer, a risk reduced by the addition of progestins. This year we have learned that the estrogen-progestin regimen increases breast cancer risk beyond the risk already associated with estrogen alone (2). Additionally, long-term HRT is associated with gall bladder disease, liver disease, increased thromboembolic events and the various cancers already mentioned. With the many natural options available, and increasing positive clinical data, healthcare professionals should no longer limit their patients' options to conventional HRT. Clearly there are cases where HRT may be the best option for an individual woman, but only when other options have been ruled out. Let us overview some of these other options.

Natural Approaches

It is important to properly assess the needs of the patient and their desired outcome. As menopause is viewed and experienced differently by each woman, it is critical to develop a protocol that reflects her desire for improved quality of life and one that takes into consideration her risk factors for diseases in which no symptoms yet appear.

Diagnosing Perimenopause

Perhaps one of the most important aspects of treating menopause is knowing exactly where in the process the patient is. That is, diagnosing whether the patient is endogenously cycling, ovulating, or fully post-menopausal. What is her progesterone to estradiol ratio? One of the best and simplest ways to answer these questions is with salivary hormone analysis. The use of salivary free-fraction analysis of steroid hormones like estrogens, progesterone, cortisol, and DHEA is not only becoming more common, it is becoming the preferable way of measuring these hormones (3).

At the early stages of perimenopause, luteal phase deficiencies may lead to reduced progesterone production and irregular bleeding when compared to normal pre-menopausal patterns. Since estrogen production often does not fall until 6 months before the final menstrual period, this can lead to an estrogen dominant phase within perimenopause (this is also typical in fully post menopausal women). Since it is best to keep the progesterone:estrodiol ratio within a 20:1- 30:1 ratio, knowing both the estradiol and progesterone levels is beneficial to selecting the proper therapy. It is relatively easy to give natural progesterone in sublingual, oral or cream forms to bring this ratio into balance. When the patient is confirmed postmenopausal, a single salivary sample is adequate, whereas a women who is endogenously cycling should have samples taken throughout the cycle (even if she has no menses) to gather the necessary diagnostic data. Additionally, salivary cortisol, DHEA and testosterone levels will help diagnose adrenal or androgen deficiencies that may alter therapies.

Natural Hormone Replacement

After extracting either ß-sitosterol from soy or diosgenin from wild yam (*Dioscorea villosa*); these compounds can be further converted into estradiol, estrone, estriol, progesterone or DHEA. These are identical to the structures made endogenously and can be used therapeutically. A popular practice of many physicians is the compounding of natural estrogens into a Tri-estrogen formula (Tri-Est). Most often this consists of a compound that is 80% estriol, 10% estrone and 10% estradiol. A typical formula provides 1mg estriol, 0.125 mg estrone and 0.125 mg estradiol with 40 mg of micronized oral progesterone. A Bi-Est formula is also used and eliminates the estrone component. Many researchers feel that the balance between these various hormones allows for the most natural kind of hormone replacement therapy. Physicians should talk to a compounding pharmacist for more details on this form of therapy. (See progesterone sidebar for more information on progesterone therapies).

Diet and Supplementation

There is certainly enough to be said about a proper diet through ones lifetime, and several extremely popular diets exist. Suffice it to say that before dealing with any of the complex symptoms that are associated with menopause it is important to know that each patient's metabolism is able to perform its required functions; not hindered by a lack of vitamins, minerals, calories, essential fatty acids etc. A daily regimen to include a quality multivitamin and mineral supplement as well as supplemental oils like flax, evening primrose and fish oils should be considered as a baseline for additional supplements. Additionally, foods containing phytoestrogens may be able to significantly alter several of the immediate symptoms and risk factors associated with menopause (see phytoestrogen insert). Positive, but limited research has been conducted with hesperidin (a bioflavonoid) and vitamin C, vitamin B6, evening primrose oil and gamma-oryzanol (a ferulic acid compound isolated from rice bran oil). Gamma-oryzanol at 300mg/day for 8 weeks was able to reduce climacteric complaints 85% (Kupperman Index) and significantly reduce total cholesterol, triglycerides and increase HDL cholesterol in cases with hyperlipidemia (53).

Botanicals

Many herbs and herbal extract have been used to help alleviate the symptoms associated with the climacteric. We will discuss some of the more common ones here, and briefly mention a few more that you may come into contact with.

Black Cohosh

Black Cohosh (*Cimicifuga racemosa*) is a plant native to eastern North America. The root and rhizome portion had been used by Native Americans, who dubbed it "squaw root", long before its introduction to settlers and western herbalist. The pharmacological and clinical research of the past several decades has made it the most widely used natural alternative to hormone replacement therapy in the western world. The German Commission E has

PROGESTERONE - The forgotten hormone of menopause

Probably the most common misconception about menopause is that it is fundamentally an estrogen-deficiency disease. While there is no doubt that menopause is associated with a dramatic (40-60%) drop in estrogen production, many of the menopausal symptoms begin well before the drop in estrogen levels (which occurs 6-12 months before the final menstrual period). This has led many researchers to suspect that the hormone balance, in particular between estrogen and progesterone, may have more to do with many of the symptoms associated with menopause than the absolute levels of estrogen. The individual who has been leading this view publicly is John R. Lee M.D. His books *Natural Progesterone* (for physicians), and *What your doctor may not tell you about menopause* (for general audiences) details the wide-ranging misconceptions that have led to the medical approach that has emphasized estrogen and forgotten progesterone, much to the detriment of the women experiencing menopause.

Progesterone is a hormone produced largely by the corpus luteum of the ovary, primarily after ovulation. Progesterone ensures that the endometrium is sufficient for the implantation of a fertilized egg. If fertilization does not occur, progesterone (and estrogen) quickly drops to allow for the endometrial lining to release causing menstration to occur. If no ovulation occurs, progesterone levels never rise and the second half of the menstrual cycle (luteal phase) is in a state of estrogen dominance. The frequency of anovulatory cycles increases through perimenopause, well before estrogen begins to drop and leads to prolonged periods of estrogen dominance (when compared to progesterone).

It is vital to know what the progesterone:estradiol ratio is before diagnosing and treating menopausal women. The best way to do this is simply by a salivary hormone test, currently available through many labs (see main article "Diagnosing perimenopause"). Salivary progesterone to estradiol ratios should be 22:1 to 30:1 in post menopause. It is common to see women well below this ratio and in need of progesterone therapy. Progesterone therapy is very simple using sublingual drops, transdermal creams or orally (micronized progesterone is preferable if using oral dosing).

Natural progesterone, unlike the synthetic progestins, has no known side effects when taken at or near physiological doses. Physiological (rather than pharmacologic) doses are much smaller and intended to bring hormone levels into normal ranges rather than using these hormones as drugs. These levels can be accomplished by 100 mg per day oral, 25-50 mg per day sublingual or 20-30 mg per day of a transdermal cream. These doses reflect a general regimen and should be adjusted by the actual progesterone:estradiol ratios and the familiarity with the dose regimen of the product selected. It should be noted that while natural progesterone can be made from diosgenin extracted from wild yam, this conversion is only known to take place in the laboratory, not in the body. One should ensure that the product being used actually contains a specified level of progesterone, not merely a wild yam or other extract.

There are advantages and disadvantages to each mode of therapy. Oral dosing is familiar to most women, but more progesterone is needed to compensate for first pass liver metabolism, putting extra burden on the liver. Sublingual drops help bypass the first pass metabolism and while absorption is fast, elimination is also fast and requires divided daily doses. Trans-dermal creams absorb well through the skin and need only one or two applications per day but it is much easier to dose too heavily when taking creams (women forget to measure or think that "1/4 teaspoon just doesn't look like its enough"). Regardless of the product selected, retesting for salivary hormones should be performed after 6 months of treatment to assess hormone balance.

It would be extremely informational for anyone treating menopausal women to review the books written by Dr. Lee. These raise interesting questions concerning the role of progesterone in heart disease, osteoporosis and many of the vasomotor complaints associated with menopause and PMS. If much of what he has published is correct, a new understanding of menopause is on the horizon. With the safety profile associated with progesterone use, waiting for this understanding to hit the mainstream may not be in the best interest for women suffering the symptoms and current treatments for their menopausal symptoms.

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listed black cohosh as approved for PMS, dysmenorrhea or menopausal (climacteric) neurovegetative (vasomotor etc.) ailments.

The primary, and presumably, active components found in the roots of black cohosh are a group of triterpene glycosides. Among these are acetin, cimicifugoside and the often-standardized 27-deoxyacteine. Whether these compounds work like classic phytoestrogens is still under some dispute, with conflicting research data (4, 5). Much of the dispute rests in the presence or absense of the isoflavone formononetin; and whether this is a contamination of the extract or a result of differing extraction procedures or even sub-species differences. What we do know is that clinical trials of menopausal symptoms consistently show that extracts of black cohosh are able to reduce or eliminate many of the disturbing vasomotor symptoms. It seems that black cohosh is able to reduce luteinizing hormone (LH) levels in menopausal women, a result many people conclude to be an interaction directly with receptors located within the hypothalamus-pituitary region (6). LH surges are thought to participate as a main trigger for hot flashes, the main symptom relieved by black cohosh preparations.

In the early 1980's, the effectiveness of a black cohosh extract (standardized liquid) was studied using 629 patients with menopausal complaints (7). After only 4 weeks of treatment, a clear improvement was documented by 80% of the women and after 6-8 weeks 50% reported a complete disappearance of symptoms. While this study lacked a placebo control group, these observations, along with no reported dropouts due to side effects, show the kinds of affects reported by hundreds of doctors in Germany for years prior to this study. A second study compared a tablet containing a standardized extract of black cohosh (80 mg) with 0.625 mg of conjugated estrogens (Premarin) or 2 mg of diazepam, in the reduction of menstrual complaints. Each was able to significantly lower menopausal as well mood related symptoms, while only black cohosh and estrogens were able to increase vaginal epithelium proliferation. The authors conclude "the herbal treatment allows for the most risk-poor therapy with optimal effectiveness in comparison to hormones and psychopharmaceuticals, demonstrates a remarkable spectrum of action on the menopausal syndrome, has no toxic side effects, is suitable for long-term therapy, and is the medication of choice in cases of mild-to-moderate menopausal ailments" (8).

The results of this open study were later confirmed by a randomized, double-blinded study with placebo and estrogen (9). The first group was given a preparation of black cohosh extract (4 mg of 27-deoxyacteine) per day. Group 2 received 0.625 mg conjugated estrogens and group three received placebo. Results were scored using the Kupperman index (an index measuring 11 different vasomotor symptoms associated with menopause), Hamilton Anxiety scale (HAMA), and maturation indices on vaginal epithelial maturation. The results showed that the black cohosh group improved in all categories, when compared to placebo and even in relation to the estrogen group (recall that no progesterone was added). This estrogen-like potential was confirmed when the same dose was just as effective as estriol, conjugated estrogens, and an estrogen-progestin combination in improving postoperative ovarian functional deficits after hysterectomy in young women (10). While the majority of these articles are published in German journals, a few excellent review articles have been published in English (11, 12, 13, 14).

Dosing information for black cohosh has been somewhat confusing over that past decade. The original papers seem to have used daily amounts of extract yielding 8 mg of triterpenes (usually measured as 27-deoxyacteine). Most of the studies then began using half of that amount per day (4 mg) in divided doses. Recently, a manufacturer of one of the extracts suggests only 2 mg per day is needed for the affect noted with the higher amounts. This is likely due to the participation of other, non-triterpene components. A quality extract containing 2 or 4 mg of triterpenes daily is therefore recommended. Expect at least 2 weeks and often 4 weeks before symptomatic changes occur. Recall that black cohosh has primarily been shown to reduce vasomotor and vaginal symptoms, no clear research shows its relation to reducing risk factors associated with cancer, heart disease or osteoporosis. The safety of these herbal preparations have been confirmed in numerous studies, but this herb should not be confused with Blue Cohosh (*Caulophyllum thalictroides*) an herb, that if used improperly, has potential toxic effects for women and their unborn children (22).

Dong Quai

The root of dong quai (*Angelica sinensis*), also know as Chinese angelica, is a widely used remedy in Asia for a variety of female conditions, and is now becoming more popular in the United States. The roots contain a number of volatile oils and coumarins, many of which have been shown to have biological activity. The coumarin ligustilide is often used as a standardizing component, whether this is a more active component or simply a marker is not fully understood.

Traditionally, dong quai is thought to have a balancing or tonic effect on the female hormonal system as well as a beneficial effect on the cardiovascular system. Several reviews in English are available that cover the range of information available about the use of dong quai (15, 16). Dong quai is most often used in Asian remedies with a number of other ingredients. It is difficult to predict what effect dong quai is intended to have as a single ingredient. One recent report that evaluated dong quai's ability to reduce hot flashes and improve vaginal and endometrial indices failed to show any improvement (17). The failure of dong quai in this study could have stemmed from a number of issues. Primarily, the diagnostic paradigms between Traditional Chinese medicine (TCM) and Western medicine are sufficiently different to make a single preparation of dong quai at these doses difficult to assess the value of these findings. The current body of research lacks a sufficient amount of information (pharmacologically and clinically) to fully recommend a menopausal protocol that uses dong quai or its extracts alone. Whether a formula that includes dong quai will be effective for a Western diagnosis of menopause (by age, FSH or estrodiol levels), is yet to be clinically tested.

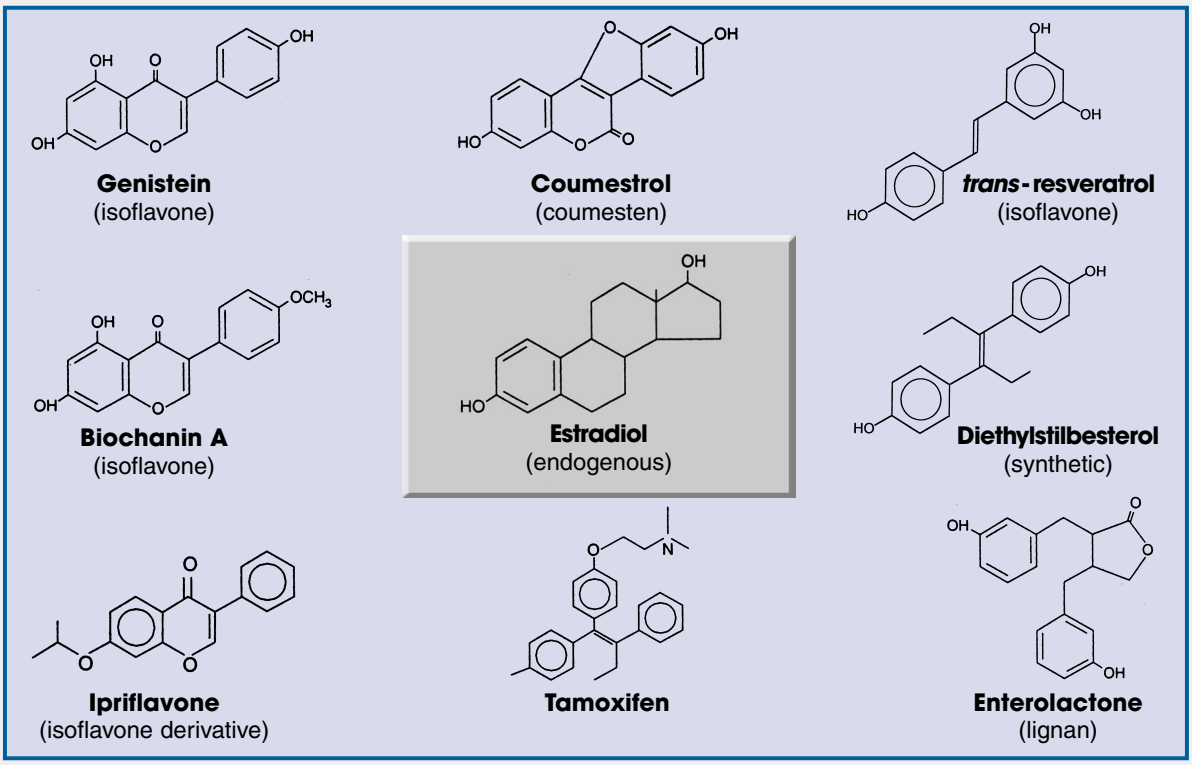
The Role of Dietary Phytoestrogens in Menopause

Phytoestrogens are plant-derived molecules that are able to activate or inhibit processes in which estrogen plays a role. Several different mechanisms may be involved, such as weak but direct binding to estrogen receptor molecules, binding or inhibiting secondary binding molecules like SHBG, or effects on the hypothalamus-pituitary access that alter estrogenic secretion. Most often, phytoestrogens have structures that are remarkably similar to the endogenous estrodiol molecule (Figure 1). The similarity has lead to a comparison (therapeutically and mechanistically) to selective estrogen receptor modulators (SERMs) (48).

There are three main classes of phytoestrogens: isoflavones, coumestans, and lignans. Figure 1 shows representative molecules in each class as well as derivative molecules used therapeutically. Once ingested, phytoestrogens undergo metabolic conversions in the gastrointestinal tract. These conversions are predominantly determined by the gastrointestinal flora (*L. acidophilus, B. bifidum* etc.). For this reason, antibiotic use, gastrointestinal infections, candidiasis or other bowel diseases can dramatically alter the bioavailability of ingested phytoestrogens (See *The Standard* Vol. 2 No. 2 for more information on probiotic uses).

Dietary phytoestrogens are found primarily in nuts, fruits and grains. The most researched and widely available phytoestrogens are those found in the soybean (*Glycine max*). Soybeans contain 1-2 mg of isoflavones per gram of soy protein, approximately 60% of which is genistein, 30% daidzein, and 10% other isoflavones. Other plants that are high phytoestrogen sources are red clover (*Trifolium pratense*, high in biochanin A), alfalfa (*Medicago sativa*) and flaxseeds (*Linum usitatissimum*, the highest source of dietary lignans). The decreased prevalence of menopausal symptoms among Japanese and other Asian cultures has lead to the speculation that much of this can be attributable to increased phytoestrogen intake (primarily in the form of soy). Additionally, cardiovascular disease and rates of hormone-related cancers such as breast and prostate cancers are also epidemiologically related to increased phytoestrogen consumption. A number of studies have been conducted to test these hypotheses.

The Menopause and Osteoporosis Center in Italy conducted an experiment in which they divided 104 postmenopausal women into two groups: one to receive 60 grams of isolated soy protein (containing 76 mg isoflavones) or 60 grams of casein (no isoflavones) each day for 12 weeks



(23). Each patient was assessed at week 4, 8 and 12 by diary entries of menopausal symptoms according to the Kupperman index. The soy group showed a significant reduction in hot flash frequencies when compared to baseline and placebo (casein). A similar study was performed using soy isoflavone extracts standardized to contain genistein and daidzein (50 mg of a 1:1 mixture per day). They found a significant decrease in both the number and severity of hot flash episodes over the 12 week study period (24). A concomitant drop in night sweats was also noted. They further noted that no change was seen between the two groups in endometrial thickness, lipoproteins, bone markers, sex hormone-binding globulin, FSH, or vaginal cytology. These results supported what many researchers had believed, that certain phytoestrogens have selective estrogen modifying activities, preventing them from increasing the types of risks associated with unopposed estrogens. Similar findings have been reported by other groups (25).

The exact role of soy isoflavones (or other phytoestrogens) in cancer prevention is difficult to assess at the present time, but current research is very promising. Current epidemiological studies taken together with both *in vitro* and animal studies suggest that several isoflavones and lignans have anti-carcinogenic activities (26, 27, 28, 29, 30). One study suggests that soy's breast cancer prevention stems from early (pre-pubertal) exposure to isoflavones that affects the proliferative potential of these tissues in later years (31). Lancet published a case-control study to test the dietary intake of phytoestrogens and breast cancer risk. They found that women in the highest quartile of urinary equol (converted from dietary intake of genestein and daidzein) and enterlactone (converted from dietary intake of lignans) had a 73% and 64% reduction in breast cancer risk respectively (32). Furthermore, the role of lignans in flaxseeds has been linked to structural changes in mammary tissues that potentially reduce mammary cancer risk (33) and flaxseed consumption in postmenopausal women altered urinary excretion of estrogen metabolites suggesting it has a chemoprotective role in postmenopausal women (47). These data, taken with similar data reflecting the protective nature of alpha-linolenic acid in breast tissues (flaxseed is the richest source of ALA) suggests that the intake of flaxseed has tremendous health potential, especially in menopausal women (not to mention the beneficial role of omega-3 fatty acids- See *The Standard* Vol.3 No. 2.).

The role of phytoestrogens in reducing atherosclerosis and other heart diseases has been under investigation for some time. Several mechanisms have been proposed for these molecules in general and specifically to the soy based genestein and daidzein molecules. They include antioxidant, anti-estrogenic, alterations in liver metabolism, inhibition of smooth muscle cells that lead to atherosclerotic progression, and suppression of thrombus formation (34-36). Lipid profiles in hypercholesterolemic patients are, in some studies, unchanged when compared to placebo (TC, TGs, LDL)(37), while others report finding hypolipidemic affects (38). Since most of these studies involved dietary intakes of soy proteins or food preparations (standardized to isoflavone content), these inconsistancies may be attributable to product variability, individual dosing variations or a result of non-isoflavone soy components. A recent study found that the isoflavones derived from red clover were able to improve arterial compliance, an index of elasticity of large arteries (known to decrease with age and menopause) (39). This experiment was conducted with a red clover extract providing 40 mg of isoflavones per day. The researchers reported a 10% drop in LDL/HDL ratios, although LDL levels themselves were not significantly reduced over placebo. It is clear that, while promising, more studies need to be done in order to assess the role of soy isoflavones or other phytoestrogens in the prevention of cardiac diseases.

For many years, estrogen replacement therapy has been the treatment of choice for improving bone mass in postmenopausal women. As with other estrogen deficiency-related conditions, osteoporosis may be a candidate for phytoestrogen intervention. Several models postulate a role for phytoestrogens in the prevention of osteoporosis but few studies have found conclusive evidence that naturally occurring phytoestrogens dramatically alter bone mass (40). One recent study showed a significant increase in both bone mineral content and density in the lumbar spine (although not elsewhere) when 40 grams per day of soy protein were taken for 6 months (37.). Animal studies using soy fed animals suggest that the isoflavone portion is required for bone sparing effects (51). Again, epidemiology would suggest that dietary phytoestrogens plays a role in preventing osteoporotic fractures, but other factors like overall diet and physical labor may play an equal role in the failure of Western women reaching peak bone mass prior to the menopausal years.

Ipriflavone

The role of naturally occurring phytoestrogens has led to the development of several phytoestrogen derivatives. One such derivative, ipriflavone, has been extensively studied and shown to be both efficacious and safe for the treatment of osteoporosis (40). While ipriflavone has little affect on other estrogen-related physiological functions, it seems capable of inhibiting bone resorption and increasing bone mineral density in elderly osteoporotic women (41). Other studies have shown that ipriflavone increases duodenal calcium transport, similar to estradiol (42). A closer look, though, suggests that ipriflavone has bone protective mechanisms that differ from estrodiol, one that involves increasing the rate of bone formation (52). Positive clinical trials have consistently used 200 mg, three times per day (600 mg/day) and have been conducted for 1 or 2 years with significant treatment vs. placebo differences (43- 46). As with each of the naturally occurring phytoestrogens, iproflavone is modified by the gastrointestinal flora. The resultant active molecule or molecules have not been fully characterized and may be similar or identical to those formed by the modification of one or more naturally occurring molecules. Ipriflavone, while not a naturally occurring isoflavone, is currently being used in dietary supplements, specifically for its ability to enhance the actions of other bone supporting and mass building substances. It should be noted that several reports have found that oral intake of ipriflavone increases serum levels of the drug theophylline (a bronchodilator used for COPD and asthma), an interaction occurring at the cytochrome P450 enzyme (49).

Phytoestrogen safety

While much praise is being heaped on this class of compounds, some cautions have been raised concerning the use of dietary phytoestrogens. As mentioned, they have both estrogenic and anti-estrogenic activities. In fact, their activity was first noted in sheep that became infertile after extensive grazing in pastures with isoflavone rich clover. How much is too much? Some researchers believe that too much emphasis has been placed on phytoestrogen consumption in Japan and other Asian countries and that other epidemiological factors are likely to be behind the reduced levels of heart disease, menopausal symptoms and various cancers. Others are concerned about the commercial nature of isoflavone producing companies (especially soy) and the role of biased scientific research to support their use. While these and other concerns should be kept in mind, on balance it seems that the role of phytoestrogens may be able to play a significant and safe role in treating menopausal-related symptoms and risk factors.

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Chaste Tree (Vitex agnus castus)

While the use of extracts derived from the ripened berries of the chaste tree have numerous uses in treating women, most often this herbal remedy is used in premenopausal women experiencing irregular menstrual complaints. One of the mechanisms proposed for vitex is an increase in LH secretion, which has a progesterone favoring effect. In the early stages of perimenopause, when cycle irregularities and slow persistant bleeding are associated with an estrogen dominant luteal phase, chaste berry extracts would be an excellent herbal choice. More on this herb and others associated with premenopausal menstrual irregularities will be covered in a future review.

Licorice Root

The major active component in Licorice root (*Glycyrrhiza glabra*) is glycyrrhizin, with minor components such as ß-sitosterol, formononetin and coumarin. These compounds have estrogenic and anti-estrogenic capabilities. Glycyrrhizin binds both estrogen and androgen receptors weakly, although it had no affinity for the progesterone receptor (18). A previous review discussed the role of licorice root extracts in supporting the adrenal gland (*The Standard* Vol. 3 no. 1), one of the likely modes that licorice helps with menopausal symptoms. Of course, high levels of licorice root extract should be cautioned in individuals with high blood pressure.

Trans-Resveratrol

Resveratrol is a naturally occurring compound abundant in grapes and other plant foods, produced by these plants under stress to protect them from environmental or pathogenic attack. The *trans* configuration is virtually the only naturally occurring isomer, and is nearly identical to the synthetic estrogen diethylstilbesterol (see figure in phytoestrogen article). This unique structure has estrogenic, antiestrogenic, antioxidant (free radical scavenging) cardioprotective and anticancer activities (19, 20, 50). The ability to act as a potential estrogenic agent, while at the same time protecting against cardiovascular risk factors, inhibiting various cancers and increasing antioxidant protection is a potent combination, especially for the combined risk factors associated with menopause.

Based on the protection gained by *trans*-resveratrol consumption from wine, dosing recommendations are in the range of 2-4 mg per day (21). *Trans*-resveratrol can be extracted from grapes or is also commercially available from rhizome extracts of *Polygonum cuspidatum*, a plant used in traditional Chinese medicine under the name *huzhang* (tiger cane). While being relatively new to the nutraceutical world, reports of *trans*-resveratrol's actions are sure to place it in the forefront of natural substances for the treatment of menopause and its related risk factors.

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Other Botanicals

Depending on where one looked, any number of botanicals are recommended for various menopausal complaints. The use of St. John's wort extracts (*Hypericum perforatum*) for depression and *Ginkgo biloba* extracts for mental acuity are frequently recommended. Preparations of valarian (*Valariana officinalis*) and passion flower (*Passiflora incarnata*) are often recommended for insomnia. Anti-anxiety and calming herbs such as hops (*Humulus lupulus*), kava kava (*Piper methysticum*) and German chamomile (*Matricaria recutita*) are often prescribed by herbalists for emotional balance when necessary. Of course in TCM and Ayervedic traditions, many herbal preparations would be used depending on the associated symptomology. Most of these herbs or herbal combinations have not been tested using currently accepted Western clinical research outcomes. It should be understood, however, that in clinical settings, many of these remedies are found to be effective by the physicians who are the most familiar with their use.

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Acknowledgement: I would like to thank Jeremy Johnson for gathering and organizing many of the references used to write this review. His assistance and discussion were invaluable and added tremendously to the content of these articles.

SUMMARY

- The role of diet, lifestyle and stress can be a large component in the experience of menopausal symptoms. Dismissing these in diagnosing and treating will result in frustration for both patient and physician.
- It is important to know the progesterone:estradiol ratio, even reduced estrogen can leave a women estrogen dominant and in need of supplemental progesterone.
- Salivary hormone tests should be done to assess ovary and adrenal hormone output (progesterone, estrogens, cortisol, DHEA).
- Vitamins, minerals and essential fatty acids need to be adequate to ensure any therapy relying on the body's own metabolic activities. The lack of these fundamentals adds unnecessary complexities to the diagnostic and treatment protocols.
- Increasing dietary and/or supplemental phytoestrogens should be considered by all women, especially those who are perimenopausal or menopausal. May include especially Soy, Red Clover, Alfalfa, Flaxseed.
- Therapeutic use of Black Cohosh providing 4 mg of triterpenes per day has been shown to significantly reduce menopause-related vasomotor symptoms.
- *Trans*-resveratol, a phytoestrogen found in grapes and other plants shows promising results as a menopausal supplement, having effects on vasomotor symptoms, antioxidant activity, bone building potential and cardiovascular benefits.
- Other supplements and botanicals have positive but limited reports on menopausal complaints and risk factors. They include: dong quai, licorice root, chaste berry extracts, Vitamin B6, gamma oryzanol, and various bioflavonoids.
- There are natural hormones and hormone combinations that are physiologically more compatible than the synthetic hormones promoted by drug companies. These should be considered before synthetic hormone replacement.
- Generalizations are often difficult. A different protocol may be required for each patient depending on symptoms, age, previous menstrual history, relative risks for osteoporosis, heart disease, breast or endometrial cancer, diet, stress, lifestyle and attitudes toward alternative approaches of treatment.

The perception of menopause has changed dramatically in the past 50 years, now the options for treating it are finally expanding within mainstream Western medicine. While hormone replacement therapies have been available and promoted heavily, only about 15% of menopausal women in the United States use these therapies. Of the 85% that remain, few alternatives have been given for relieving their symptoms. This, like other reviews, has attempted to outline those natural therapies that have been tested and proven effective at some level. Clinicians who take the time to learn about these approaches and treatments are sure to find rewarding outcomes and delighted patients.